STEREOSELECTIVE TRANSFORMATION OF CARBOHYDRATES BASED ON SILICON CHEMISTRY

Floris van Delft

STEREOSELECTIVE TRANSFORMATION OF CARBOHYDRATES BASED ON SILICON CHEMISTRY

PROEFSCHRIFT

TER VERKRIJGING VAN DE GRAAD VAN DOCTOR
AAN DE RIJKSUNIVERSITEIT TE LEIDEN,
OP GEZAG VAN DE RECTOR MAGNIFICUS DR. L. LEERTOUWER,
HOOGLERAAR IN DE FACULTEIT DER GODGELEERDHEID,
VOLGENS BESLUIT VAN HET COLLEGE VAN DEKANEN
TE VERDEDIGEN OP WOENSDAG 15 MEI 1996
TE KLOKKE 15.15 UUR

DOOR

FLORIS LOUIS VAN DELFT

GEBOREN TE UTRECHT IN 1968

Promotiecommissie

Promotor	:	Prof. dr. J.H. van Boom
Co-promotor	:	Dr. G.A. van der Marel
Referent	:	Dr. G.J.P.H. Boons (University of Birmingham, UK)
Overige Leden	:	Prof. dr. D. Bedeaux Prof. dr. A. van der Gen Prof. dr. J. Lugtenburg Prof. dr. J. Reedijk

Soms is het beter om te reizen
dan om aan te komen

Robert M. Pirsig

Table of Contents

List of Abbreviations

Ac	acetyl	*M*	molecular mass
anal.	(elemental) analysis	M	molar
arom	aromatic	*m*-CPBA	*meta*-chloroperbenzoic
b	broad		acid
Bn	benzyl	Me	methyl
Boc	*tert*-butoxycarbonyl	mp	melting point
bp	boiling point	MS	mass spectroscopy
Bz	benzoyl	*n*	normal
calcd	calculated	NBS	*N*-bromosuccinimide
Cbz	benzyloxycarbonyl	NMR	nuclear magnetic
cond.	conditions		resonance
Cq	quaternary carbon atom	nOe	nuclear Overhauser
COSY	correlated spectroscopy		enhancement
d	doublet	*o*	ortho
dd	doublet of doublets	ORTEP	Oakrich Thermal
dt	doublet of triplets		Ellipsoid Plot
DMAP	4-(dimethylamino)	*p*	para
	pyridine	Ph	phenyl
DMF	*N,N*-dimethylformamide	ppm	parts per million
DMSO	dimethyl sulfoxide	q	quartet
equiv.	equivalent	R_f	retardation factor
EI	electron impact	rt	room temperature
Et	ethyl	s	singulet
FAB	fast atom bombardment	t	triplet
Hz	herz	*t*-Bu	*tert*-butyl
i-Pr	*iso*-propyl	Tf	trifluoromethanesulfonyl
isoprop	isopropylidene	TFA	trifluoroacetic acid
IR	infrared	THF	tetrahydrofuran
J	coupling constant	TLC	thin layer
Lit.	literature		chromatography
m	meta	TMS	trimethylsilyl
m	multiplet	Ts	*p*-toluenesulfonyl

Silicon in Carbohydrate Chemistry

1. Silicon - Mildest of metals

1.1 Basic features

During the past two decades, organosilicon compounds have emerged as powerful tools for the design and synthesis of natural products[1]. Although carbon-bound silicon is not a normal constellation in naturally occurring compounds[2], its temporary presence may exert a distinct and beneficial effect on the outcome of a particular reaction or transformation *en route* to complex organic molecules.

The freely available element silicon belongs to the same periodic group as carbon and normally shares its quadricovalency. However, the differences between these elements are numerous and greatly outweigh any similarities. For instance, the relatively long carbon-silicon bond is polarized in the sense $Si^{\delta+}$-$C^{\delta-}$, placing organosilanes in the class of organometallics or organometalloids[3]. In those cases where carbon forms double or triple bonds, silicon generally forms polymers with single bonds[4]. Moreover, silicon forms strong covalent bonds to oxygen, fluorine and chlorine (Table 1), and notably the Si-F bond is one of the strongest single bonds known[5].

Tetraalkylated silanes, or organosilanes, can be easily handled and withstand a wide variety of reaction conditions. The carbon-silicon bond is quite stable towards homolytic fission, but can be cleaved by ionic reagents because silicon is more electropositive than carbon. For this reason, nucleophilic or electrophilic attack occurs at silicon or carbon,

Table 1. Typical bond lengths and dissociation energies of carbon and silicon

Bond	Length (Å)	Dissociation Energy (kJ/mol)	Bond	Length	Dissociation Energy (kJ/mol)
C-C	1.54	334	Si-C	1.89	318
C-O	1.41	340	Si-O	1.63	531
C-Cl	1.78	335	Si-Cl	2.05	471
C-F	1.39	452	Si-F	1.60	808

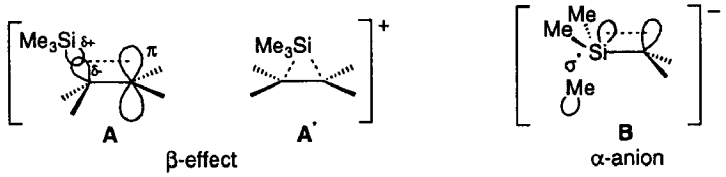
respectively. In this respect, Fleming has suggested[1a] that silicon bound to carbon should be considered as a "super-proton": cleavage of a C-SiR_3 bond by a particular ionic reagent will generally proceed more readily than the corresponding C-H bond. Silicon lacks lone-pair electrons, thus excluding coordination to electrophilic agents.

A proximate silicon group can, due to its dichotomous electron donor and acceptor properties, stabilize a negative or a positive charge and strongly perturb a π-system in a variety of molecules. The actual reactivity and selectivity of reactions involving organosilanes depends on steric and electronic effects of a particular silyl moiety. The electronic effects of an R_3Si group can be roughly subdivided[6] into: (*i*) *inductive effects*, polarizing the C-Si bond in the direction $C^{\delta-}$-$Si^{\delta+}$, (*ii*) *field effects*, depending on the σ-dipole moment of the entire R_3Si-group, (*iii*) *(p-d) π-bonding*, involving participation of the relatively low-lying and unoccupied silicon 3d-orbitals with π-type orbitals adjacent to silicon, and (*iv*) *hyperconjugative effects*, also known as *σ-π conjugation* or *vertical stabilization*. Generally, the contribution of the field effect and (p-d) π-bonding is relatively small. Moreover, the factors which influence the selectivity in reactions are probably not solely, or even largely, a result of an electronic contribution but rather a combination of electronic and other variables including steric effects. With respect to the latter, it has to be noted that the influence of the steric bulk of a particular silyl moiety is partly diminished by the relatively long Si-C bond[7] (Table 1).

1.2 The β-effect and α-anions

Because silicon is more electropositive than carbon, the occupied sp^3-type orbitals making up the C-Si bond have higher coefficients on carbon than on silicon, resulting in substantial overlap of these filled orbitals with empty p-orbitals of an adjacent carbocation (hyperconjugation). This phenomenon is known as the β-silicon effect[8] and can be represented as in structure **A** (Figure 1). Alternatively, non-vertical stabilization of carbocations, entailing cyclic structure **A'**, has been suggested[9] for representation of the structure of the cation on the basis of kinetic α secondary isotope effects. It remains unclear[10], however, if the bridged ion **A'** concerns an absolute energy mininum or a low

Figure 1. Stabilization of a β-cation or an α-anion by silicon



maximum, although **A'** is generally accepted as transition structure during 1,2-silyl shifts.

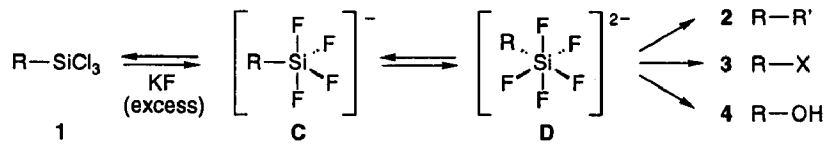
For significant overlap, the C-Si σ-bond must be able to adopt a co-planar relationship with the empty p-orbital. Accordingly, operation of the β-effect is often lowered in cyclic molecules or molecules with restricted rotation.

In spite of its electropositive character as compared to hydrogen and carbon, silicon also favours the development of α-anions[11] by stabilization of the carbon-metal bond as depicted in structure **B** in Figure 1. In this case, backdonation of the filled sp^3-orbital at carbon to the empty σ^*-antibonding orbitals of the C-Si bond is presumably responsible for the stabilizing effect. Earlier explanations of the silicon α-effect were based upon overlap of the sp^3-electrons with the empty silicon 3d-orbital, but this view has been abandoned[12].

1.3 Tetra-, penta- and hexacoordination

Under normal circumstances, the organosilanes used in organic synthesis entail tetracoordinated silicon. One of the useful aspects of silicon for organic chemistry is the potential of silicon to form penta- and hexacoordinate species[13] in the presence of fluoride-ions or other Lewis bases, *e.g.* a solvent. For instance, treatment of trichlorosilane **1** with excess fluoride ions produces the pentacoordinate anionic silicon species **C** (Scheme 1) in a fast and reversible manner. Due to the electron-withdrawing effect of the additional fluorine, the pentacoordinate silicon has become more electrophilic, thus promoting attack by the nucleophilic agent to give the alkylpentafluorosilicate **D**, the

Scheme 1



structure of which has been confirmed[14] by ^{19}F NMR spectroscopy. These double-negatively charged and coordinatively saturated organosilanes are versatile intermediates in organic synthesis. Structure **D** can undergo a variety of synthetic transformations[15],

including palladium(0)-mediated coupling[16] with alkyl- and arylhalides (R'X) to give **2**, halogen- and copper-mediated conversion[17] to give the organic halides **3**, and most notably, oxidative cleavage[18] with *m*-CPBA or H_2O_2 to the alcohols **4** (*vide infra*).

2. Silicon in Organic Synthesis

The unique properties of silicon opened the way to the development of a wide variety of synthetic methods, the vast majority of which are based on two main properties of silicon, *i.e.* the formation of a strong covalent bond to oxygen or fluorine and the β-silicon effect. Silicon-containing compounds have also found extensive use in carbohydrate chemistry, *e.g.* the use of silicon-based protective groups. In addition, silicon tethers have proven to be of high value for the construction of glycosidic linkages. It is also of interest to note that trimethylsilyl triflate is an efficient promoter for glycosylations. Apart from this, oxidative cleavage of the carbon-silicon bond is a promising tool in the synthesis of higher-carbon and branched sugars. The next section will discuss some uses of organosilanes in organic synthesis that are relevant to the research described in this Thesis.

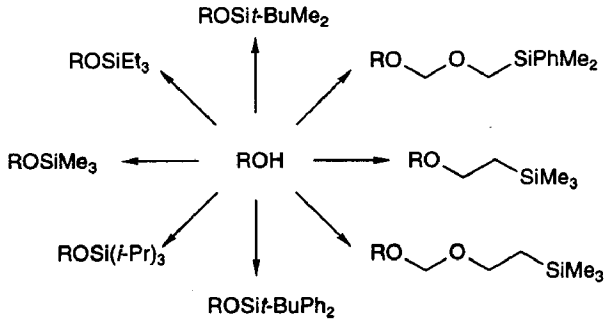
2.1 Protective groups

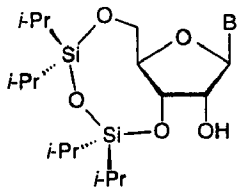
Silyl ethers provide one of the most important sets for orthogonal protective group strategies to emerge in the last twenty years. Nowadays, silyl protective groups are probably used more than any other for the protection of alcoholic functions[19]. Similarly, enols, ketene acetals and carboxylic acids can be protected by silyl-based blocking groups. The same holds for thiols, amines, amides and *N*-heterocycles, although Si-S and Si-N bonds are much more labile. Trimethylsilyl protection of terminal alkyne groups is a valuable asset in acetylene chemistry. Representative examples for the protection of alcohols are depicted in Figure 2. Among the most widely applied silyl protective groups are the trimethylsilyl (TMS), the *tert*-butyldimethylsilyl (TBDMS), and the *tert*-butyldiphenylsilyl (TBDPS) groups. A large variety of analogues has been developed[20] including protective groups for diols. In this respect, the use of the 1,1,3,3-tetraisopropyldisiloxanylidene (TIPDS) group for the protection of the 3',5'-diol function in ribonucleosides has proven of particular value in nucleic acid chemistry.

Due to the fact that the inherent stability of a silyl group can be fine-tuned by simply varying the substituents on silicon[21], silyl groups are ideal, as mentioned before, to function as orthogonal protective groups. Moreover, much of the popularity of silyl groups may be contributed to the ease of introduction and selective deprotection, *i.e.* cleavage is mildly effected by fluoride ions.

Alkyl protective groups with an internal C-Si bond have also been developed. For instance, the trimethylsilylethyl (TMSEt) and 2-(trimethylsilyl)ethyloxymethyl (SEM)

Figure 2. Some typical silyl-based protecting groups





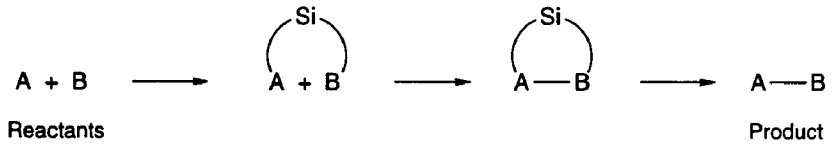
TIPDS-protected ribonucleoside

group show high stability, but can be selectively cleaved under the influence of HF in acetonitrile with concomitant formation of TMSF and ethylene. The TMSEt-group has been applied for the protection of anomeric centers in sugars[22] and for relatively acidic hydroxyl functions, *e.g.* carboxylic acids, phosphates and phenols. In the latter cases cleavage is effected with TBAF under neutral conditions.

2.2 Silicon tethers

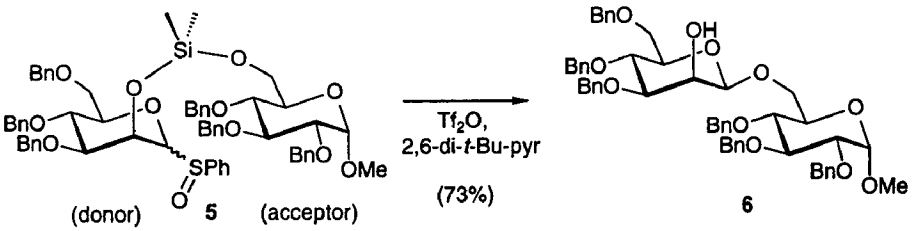
Temporary silicon tethers have been used extensively to perform intramolecular reactions[23]. In those cases that intermolecular reactions proceed with low yield and stereoselectivity, intramolecular reactions of the same type often display a higher degree of regio- and stereoselectivity. An elegant application of this strategy comprises the prior introduction of a temporary silicon tether between two individual reactants (Scheme 2).

Scheme 2



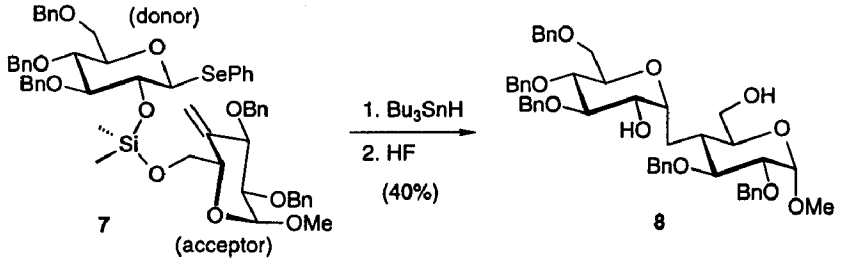
An illustrative example[24] using a dimethylsilyl acetal as a tether entails the synthesis of β-mannosidic linkages *via* nucleophilic delivery of the acceptor. Due to the axial hydroxyl at C-2 in mannose, it is notoriously difficult to construct a β-glycosidic bond with conventional glycosylation techniques[25], *i.e.* the α-products are primarily or solely obtained. By the temporary installation of a silicon tether, the acceptor is forced in a position above the plane of the mannosidic donor. For instance, activation of sulfoxide **5** (Scheme 3) with Tf_2O in the presence of base leads to the formation of an oxycarbenium ion. The β-coupled disaccharide **6** is formed by intramolecular nucleophilic attack of the C-6 oxygen of the acceptor, proceeding with concomitant hydrolysis of the O-Si bonds.

Scheme 3



In a similar approach, Sinaÿ *et al.*[26] used a silicon tether for the construction of *C*-glycosidic linkages by radical cyclization. Silaketal **7** (Scheme 4) was prepared from the suitably protected monosaccharide sub-units and dichlorodimethylsilane. Slow addition of Bu_3SnH followed by desilylation (aqueous HF) led to the formation of α-*C*-disaccharide **8** as a single diastereomer (40% yield). It was also established that the stereoselectivity of the coupling can be inverted by varying the position of the silicon tether, *e.g.* tethering at the C-4 hydroxyl of the acceptor afforded solely the β-coupled product[27].

Scheme 4



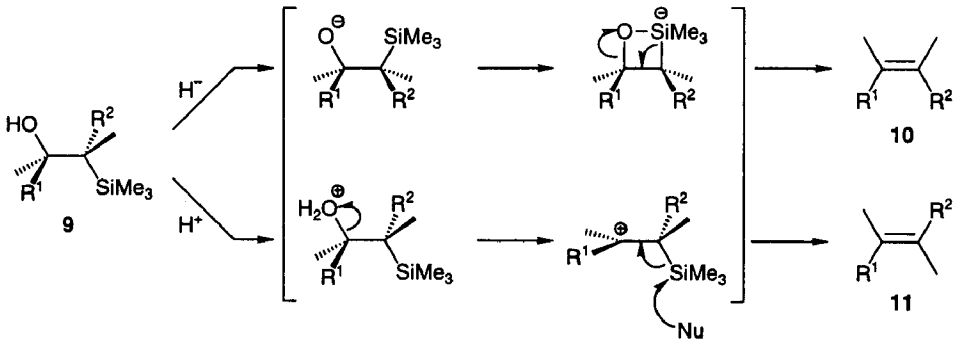
2.3 Elimination of β-hydroxy silanes

In general, organosilanes carrying a potential leaving group at the β-position can undergo 1,2-elimination[28]. In cases where the β-substituent is a hydroxyl, the elimination step can be directed in a *syn*- or *anti*-manner by performing the reaction under basic[29] or acidic[8b,30] conditions, respectively (Scheme 5). Thus, treatment of β-hydroxy silane **9** with KH affords the cis-alkene **10** stereospecifically by *syn*-elimination of trimethylsilanol.

In contrast to the concerted mechanism of the base-induced elimination, the acid-mediated reaction involves two distinct steps. Initial ionization of the C-O bond, oriented *anti*-periplanar to the silyl moiety, leads to the trans-substituted alkene **11** *via* a silyl-stabilized carbonium intermediate.

A straightforward preparation of β-hydroxy silanes entails nucleophilic addition of an organometallic reagent Me_3SiCH_2M (M=MgCl, Li) to a carbonyl compound[5a,28,31].

Scheme 5

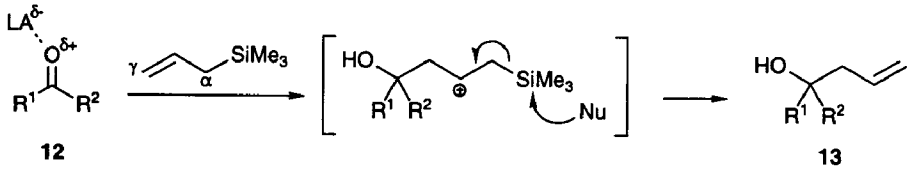


Subsequent elimination provides an attractive two-step procedure known as Peterson olefination, which is an alternative for the Wittig methylenation of aldehydes and ketones. Moreover, the unfavourable basic nature of the organometallic reagents can be circumvented by use of the organocerium analogues[32], readily accessible by precomplexation of the organometallics with $CeCl_3$. Alternative procedures for the preparation of β-hydroxy silanes comprise the reduction of β-keto silanes[33] or cuprate additions to α,β-epoxy silanes[34].

2.4 Allylation of electrophiles (Sakurai-Hosomi reaction)

Allylsilanes are excellent reagents for the formation of C-C bonds[35]. First, under the influence of a Lewis acid (LA), allylsilanes react with a variety of electrophiles in an S_E2'-type reaction[36]. For instance, carbonyl compound **12** (Scheme 6) leads to homoallyl alcohol **13** *via* a silyl-stabilized cationic intermediate, generated by attack of the activated electrophile **12** at the γ-carbon of the allyl system.

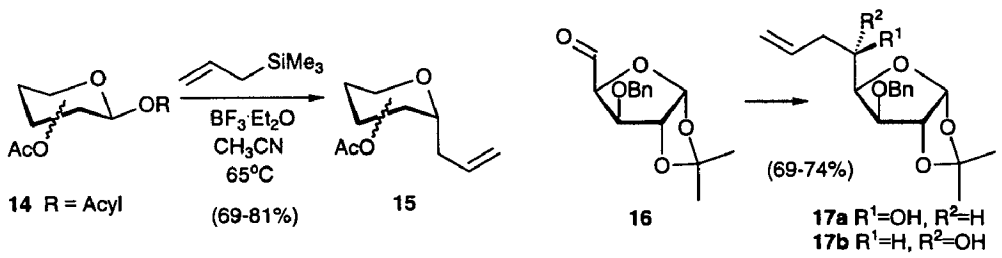
Scheme 6



In an alternative way, allylsilanes may react by a push-pull mechanism[37] (not depicted), comprising prior activation of the allylsilane by addition of a nucleophile (*e.g.* F^-), leading to an pentavalent and negatively charged silyl moiety.

The usefulness of the Lewis acid-mediated procedure is nicely illustrated[38] in the preparation of α-*C*-pyranosides (**15**) *via* stereoselective $BF_3{\cdot}Et_2O$-mediated allylation at the anomeric center of fully acylated sugars **14** (Scheme 7).

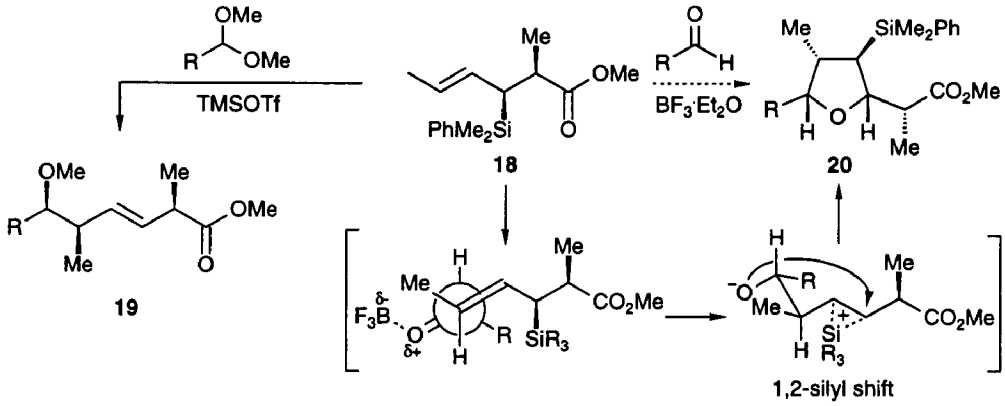
Scheme 7



It was also established that the stereoselective outcome of the allylation of α-alkoxy substituted aldehydes can be controlled by varying the nature of the Lewis acid. For example[39], allylation of xylose aldehyde **16** under the influence of $BF_3{\cdot}Et_2O$ or $TiCl_4$ gave the *anti*-adduct **17a** or *syn*-adduct **17b**, respectively, in diastereoselectivities exceeding 95%.

In contrast to the substrate directed stereoselectivity of the allylation reaction described above, the *enantioselective* addition of chiral silanes to achiral electrophiles is a valuable asset for asymmetric synthesis[40]. In this respect, Panek *et al.* extensively investigated[41] the preparation of enantiomerically pure compounds by nucleophilic addition of chiral (E)-crotylsilanes (**18**, Scheme 8) to activated acetals and aldehydes. The homoallylic ethers **19** were obtained with high diastereoselectivity upon addition of **18** to acetals. Allylation of aldehydes, however, did not afford the expected homoallyl alcohols, but tetrahydrofuran derivatives[42] of type **20**. The latter findings indicated that initial addition of the electrophile is followed by a stereospecific 1,2-silyl shift[43], presumably involving a bridged ion as in structure **A'** (Figure 1), and heterocyclization by nucleophilic attack of the alkoxide. Similar 1,2-silyl shifts of cationic intermediates were observed by Fleming *et al.*[44], as well as in a novel [3+2]-annulation process of allylsilanes with α,β-unsaturated ketones[45].

Scheme 8

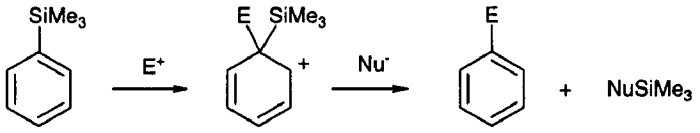


2.5 Protodesilylation of arylsilanes

A potentially acidic proton of an aryl group can be masked by a trialkylsilyl group[46]. The base-stable silyl group can be removed by treatment of an arylsilane (*e.g.* phenyltrimethylsilane, Scheme 9) with an electrophile. *Ipso*-substitution results in the formation of the deprotected aryl group *via* a silyl-stabilized cationic intermediate.

During protodesilylation, the silyl moiety is converted into a hetero substituted silane, *e.g.* a chloro- or fluorosilane. The latter silanes can undergo a variety of synthetic transformations *via* an extracoordinated species (Scheme 1).

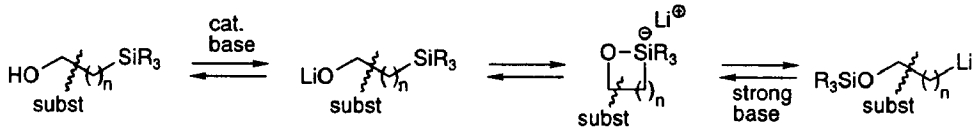
Scheme 9



2.6 Rearrangement reactions

Organosilanes which contain hydroxyl or other oxygen containing functionalities at particular positions can undergo several types of rearrangement[43]. Particularly, the base-catalyzed rearrangement of hydroxy silanes has been well-studied and [1,2]-, [1,3]-, [1,4]- and [1,5]-silyl migrations, generally referred to as Brook rearrangements, have been reported (Scheme 10). Driving force of the reaction is the formation of a strong Si-O bond at the expense of a weaker Si-C bond. Thus, treatment of hydroxy silane **21** (n=0-3) with catalytic base gives the alkoxide **22**. Intramolecular nucleophilic attack of the alkoxide at silicon produces the pentacoordinate silane **23** which rearranges to the carbanion **24**.

Scheme 10

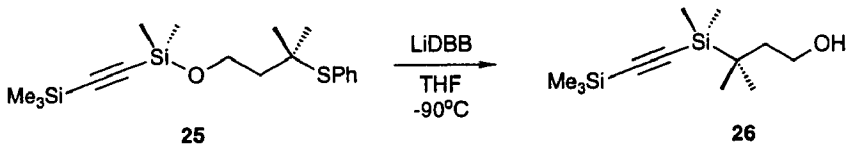


21 **22** **23** **24**

With excess of a strong base, the reverse reaction is sometimes also possible, as established for the [1,2]- and [1,4]-retro Brook rearrangement[47]. In this case, the process is driven to completion by the stability of the alkoxide anion product relative to the carbanion starting material. An elegant application of the [1,4]-retro Brook reaction was described[48] by Vasella *et al.* in the preparation of DOPS-protected alkynes (Scheme 11). Generation of a tertiary carbanion at C-3 of the alkoxy group in **25** by treatment with

lithium 4,4'-di-*tert*-butyl-biphenylide (LiDBB) at low temperature resulted, *via* retro Brook rearrangement, in the formation of alcohol **26**, a crucial building unit in the orthogonal protective group strategy aimed at the synthesis of cellulose analogues.

Scheme 11

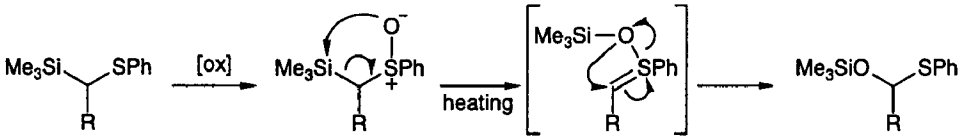


25 **26**

Acid- or Pd(0)-mediated rearrangement of α,β-epoxy silanes[49,50] is also feasible and has been applied in the synthesis of aldehydes.

Finally, migration of silicon from carbon to oxygen occurs with α-alkylthiosilanes in a Pummerer-type rearrangement[51], as depicted in Scheme 12. After partial oxidation of the sulfide **27**, the resulting sulfoxide **28** rearranges to the α-trialkylsilyloxy thioether **29** upon reflux in benzene.

Scheme 12



27 **28** **29**

2.7 Miscellaneous aspects

The above described applications of silicon are not complete. Other uses of silanes in organic chemistry[1,5] comprise (a) metal-catalyzed hydrosilylation of carbonyl functions[52] and alkenes[53], (b) Lewis acid-mediated nucleophilic addition of silyl enol ethers[54] and ketene acetals[55] to electrophiles and (c) organic transformations of vinyl- and alkynylsilanes. A variety of silicon compounds have also found application as versatile reagents in organic synthesis[5b], *e.g.* trimethylsilyl triflate as a Lewis acid and silanes as hydride donors. The possiblity of introducing chirality in silanes was already recognized in the early sixties[56]. Nevertheless, the chirality transfer of stereogenic silanes to carbon is diminished by the extended C-Si bond[7,56].

An intriguing and versatile aspect of organosilanes comprises the transformation of carbon-silicon bonds into other functionalities *via* the earlier mentioned hypercoordinated silicon, *e.g.* the hydroxyl function[18].

3. Silicon groups as masked hydroxyl functions

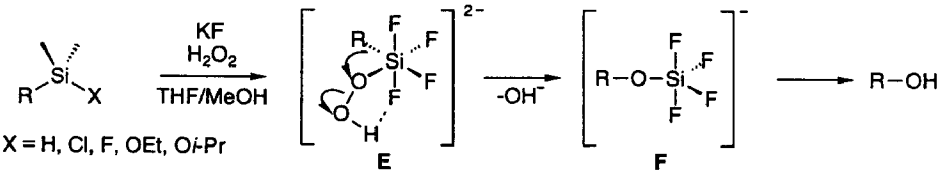
$$[si] \equiv OH$$

3.1 Oxidative cleavage of the carbon-silicon bond

In the early eighties, Tamao and Kumada *et al.*[57] as well as Fleming *et al.*[58] described the conversion of particular silyl moieties into the corresponding alcohol *via* oxidative cleavage of the carbon-silicon bond. It became apparent that a silyl moiety could also function as a synthetic equivalent of a hydroxyl group, paving the way for a whole new area of possibilities in silicon chemistry. The more so because trialkylsilyl groups possess several complementary properties as compared to a (protected) hydroxyl group, particularly in terms of size, electronegativity, stabilizing effects and lone pair electrons. It was demonstrated[58] that oxidative unmasking of silanes proceeds stereospecifically to the corresponding alcohols with *retention of configuration* at carbon. Oxidation of the carbon-silicon bond has recently been reviewed[18].

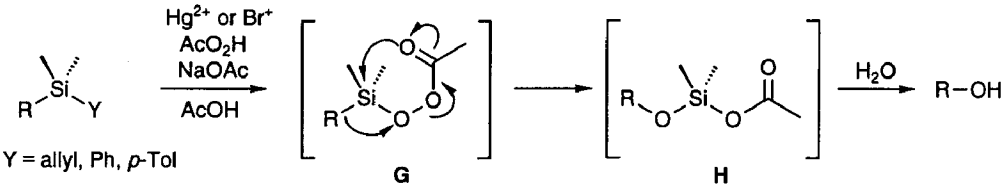
A variety of substituted organosilanes (X=H, Cl, F, OR') were developed as masked hydroxyl groups. Oxidative conversion to the alcohol ('unmasking') can be effected using one of Tamao's procedures[57,59] typically entailing treatment with H_2O_2 and $KF/KHCO_3$ in a refluxing mixture of THF and MeOH (Scheme 13). The mechanism of the reaction[59b], although susceptible to debate[60], proceeds through a hexacoordinated silicon intermediate **E**, which rearranges to the pentavalent alkoxysilane **F**. *In situ* solvolysis of labile silane **F** affords the alcohol.

Scheme 13



Oxidative unmasking of carbon-substituted silanes, *i.e.* X = allyl or X = phenyl, has been investigated by Fleming *et al.*[58,61] as well as others[57,62]. Thus, protodesilylation of the X-group is effected[58a] with HBF_4 or TFA to give the corresponding fluoro- (X = F) or trifluoroacetoxysilane (X = CF_3CO_2), respectively. Subsequent oxidative unmasking by treatment with H_2O_2 or *m*-CPBA in the presence of triethylamine affords the corresponding alcohol. A one-pot procedure for unmasking of arylsilanes[58b] (Scheme 14) comprises *in situ* mercuro- or halodesilylation under oxidative conditions (peracetic acid). *Ipso*-substitution at the aryl ring and displacement of the resulting nucleofugal group at

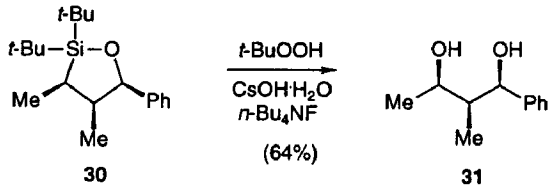
Scheme 14



silicon by attack of peracetic acid anion affords the tetracoordinated peracetoxysilane **G**, which rearranges to the labile acetoxysilane **H** in analogous fashion as for organoboranes.

A variety of other unmasking conditions have been reported, including electrochemical oxidation of α-silyl ethers to acetals[63] and unmasking of alkoxysilanes with trimethylamine-*N*-oxide[64] or oxygen in the presence of hydroquinone[65] or a flavin catalyst[66]. Very recently, Woerpel *et al.* showed[67] that the same transformation can be effected by treatment of alkoxysilanes with *tert*-butyl hydroperoxide and cesium hydroxide in DMF. The latter process is successful even in spite of the steric hindrance around silicon, allowing unmasking of sterically congested silanes such as the di-*tert*-butylsubstituted silane **30** (→**31**, Scheme 15). Moreover, the procedure allows a one-step unmasking of phenylsilanes, as well as trimethylsilanes, while the necessity of the sometimes unfavourable electrophilic conditions for protodesilylation is circumvented[68].

Scheme 15

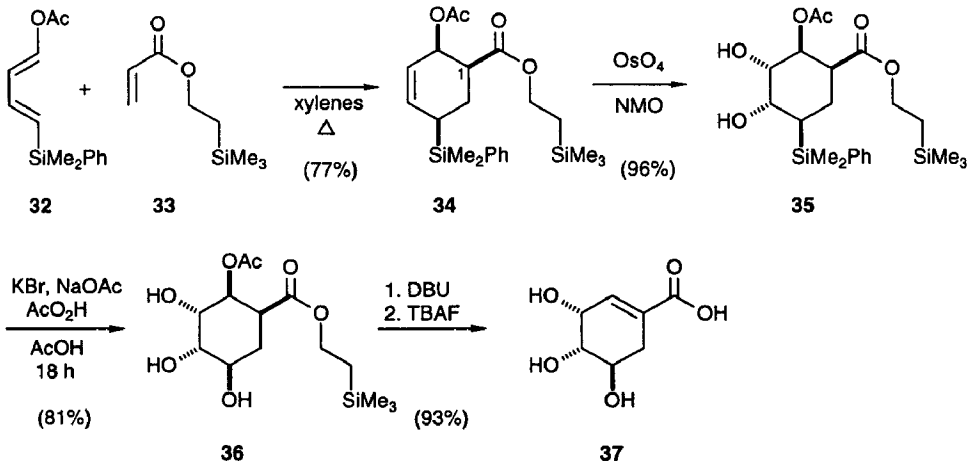


The merit of a silyl moiety in organic synthesis is illustrated[69] by the preparation of shikimic acid, a pivotal intermediate in the biosynthesis of a number of biologically important natural products (Scheme 16). Diels-Alder reaction of the vinylsilane **32** with TMSEt-protected acrylic acid (**33**) gave the all-cis cyclohexene adduct **34**, contaminated with a minor amount (7%) of the C-1 epimer. Dihydroxylation of **34** with OsO_4 proceeded with high diastereoselectivity to give **35**, the phenylsilyl group of which was unmasked with KBr and AcO_2H, to give triol **36** in excellent yield. Finally, elimination of the acetate with DBU and deprotection of the TMSEt group with TBAF gave (±)-shikimic acid (**37**).

3.2 Silyl-based masked hydroxyls

To date, most attention has been focussed on the use of alkoxy- or arylsubstituted silanes. The alkoxysilanes are unmasked under mild conditions but are often thermally and hydrolytically unstable. Arylsilanes, on the other hand, are compatible with a wide variety

Scheme 16

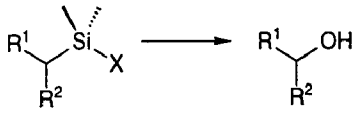


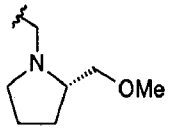
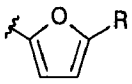
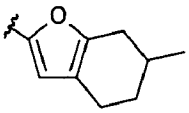
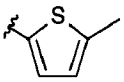
of reaction conditions, but have the drawback that the unmasking conditions are incompatible with electron-rich functional groups such as amines, sulfides and internal double bonds[61]. In order to avoid the undesirable electrophilic conditions, a variety of dimethylsilyl-based masked hydroxy groups has been developed (Table 2), the vast majority of which took their inspiration from the findings of Tamao or Fleming. The only exception concerns the (trimethylsilyl)dimethylsilyl group[70,71,72] (Entry 6) unmasking of which could be executed with TBAF and oxygen[70]. The chiral pyrrolidine subunit (Entry 5) deserves special attention as it was used for the highly enantioselective synthesis of diols[73]. Taber *et al.*[74] circumvented the electrophilic conditions in the unmasking of phenylsilanes *via* Birch reduction in the first step (Entry 4). The furyl[75,76,77] and thienylsilanes[78] (Entries 7-9) are smoothly unmasked under Tamao conditions. However, the intrinsic lability of this type of silanes limits their general applicability in organic synthesis. Finally, the phenylthio(cyclopropyl) substituted silanes of Landais *et al.* (Entry 10) are stable under a variety of conditions and are elegantly unmasked in a three-step procedure *via* sila-Pummerer rearrangement[79].

The examples collected in Table 2 are characterized by the presence of two methylgroups on silicon. It was found[47d,57,80] that unmasking of silyl moieties carrying more sterically congested alkyl substituents is often cumbersome or impossible. Nevertheless, a variety of silyl groups with other substitution patterns also undergo unmasking[18], including di- and trifluorosilanes, trichlorosilanes, di- and trialkoxysilanes, triphenylsilanes, hydroxyphenylsilanes and tris(trimethylsilyl)silanes.

Of special interest is the allylic diphenylsilane **38** (Scheme 17), which can be readily introduced by nucleophilic addition of its anion to an electrophile, and unmasking of the allyldiphenylsilyl moiety is compatible with other double bonds in the molecule[81]. The same holds for Tamao oxidation of the (dimethylamino)silanes **39** (n=1 or 2), the anions of which are the first reported 'functionalized' silyl anions[82].

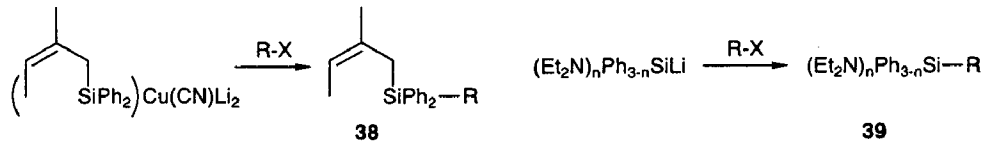
Table 2



Entry	X		Demasking Conditions	Reference
1	H, Cl, F, NEt_2 OMe, OEt, O*i*-Pr, O*t*-Bu		H_2O_2, KF, $KHCO_3$	57,59
2	Allyl		1. E^+ 2. Tamao[a])	57,62
3	Ph, *p*-CH_3Ph		HgOAc or Br_2, AcO_2H, AcOH	58,61
4	Ph		1. Na, NH_3 2. TBAF 3. Tamao[a])	74
5			Tamao[a])	73
6	$SiMe_2R$	R=Me	TBAF, O_2	70
		R=Me	1. $AlCl_3$ 2. Tamao[a])	71
		R=Ph	1. TBAF 2. Tamao[a])	72
7		R=H	1. TBAF 2. *m*-CPBA	75
		R=Me	1. $^1O_2$, hv 2. Tamao[a])	76
8			1. TFA 2. Tamao[a])	77
9			1. TBAF 2. Tamao[a])	78
10			1. $NaIO_4$ 2. PhH, reflux 3. Tamao[a])	79

[a]) Entailing treatment with H_2O_2, KF, and $NaHCO_3$ in THF/MeOH or a variation thereof

Scheme 17



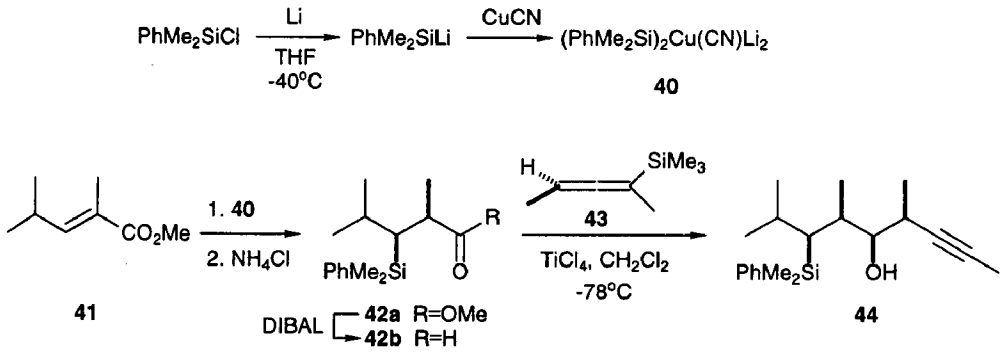
3.3 Hydroxylation

The variety of procedures for the introduction of a silyl moiety into an organic compound further extends the versatility of the use of silicon in chemistry. For example, conversion of a chlorosilane to the corresponding anion by metal-halogen exchange affords the corresponding silyl anion as a nucleophilic species. In a reversed fashion, electrophilic silylation can be effected by addition of a nucleophile to a chlorosilane. In addition, the metal catalyzed intramolecular hydrosilylation of double bonds has been reported, as well as carbenoid insertion to silanes.

Silyl anions, although known for over 40 years[83], have received minor attention. In 1958, Gilman *et al.*[83b,c] found that metal-halogen exchange of chlorodimethylphenylsilane and lithium (Scheme 18) led to the formation of $PhMe_2SiLi$. Subsequent complexation of the silyllithium reagent with CuCN gives the mixed cuprate **40**[84], which has been applied extensively by Fleming *et al.*[61a]. Nucleophilic addition of **40** proceeds smoothly with a wide variety of electrophiles including enones or α,β-unsaturated esters, acetylenes, allylic acetates, allenes, epoxides and alkylbromides. Other silyl anions[85] that have been applied, with various counter ions, include Ph_3Si^-, Me_3Si^-, $(Me_3Si)_3Si^-$ and $Me_3SiMe_2Si^-$. Recently, Tamao *et al.*[82] prepared the first 'functionalized' silyl anion (*vide supra*).

The usefulness of silyl anion **40** as a synthetic equivalent of the hydroxyl anion is nicely illustrated in a model study[86] of Fleming *et al.* towards the stereoselective preparation of ebelactone A, an esterase inhibitor. Conjugate addition of cuprate **40** to

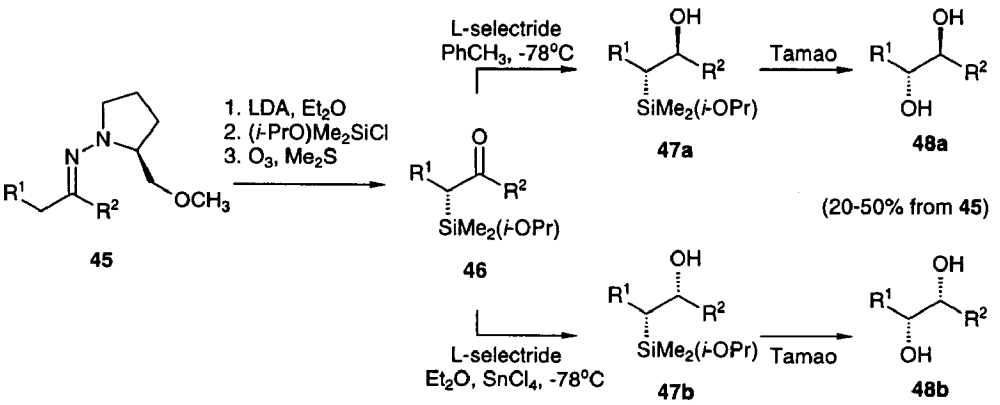
Scheme 18



α,β-unsaturated ester **41** and subsequent stereoselective protonation gave the β-silyl ester **42a** with 92% diastereomeric excess. Condensation of aldehyde **42b**, obtained by partial reduction of **42a**, with allenylsilane **43** proceeded highly diastereoselectively to give adduct **44**, forming 73% of the mixture of four possible diastereomeric products.

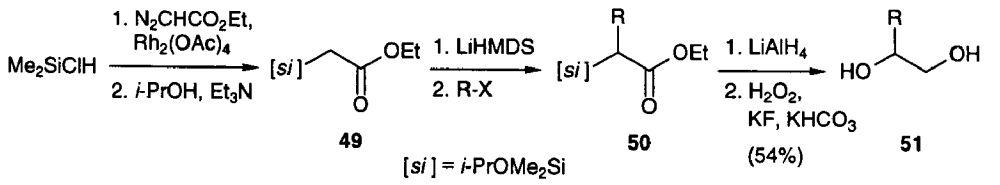
In contrast to silyl anions, chlorosilanes show electrophilic behaviour. For instance, Enders *et al.*[87] used chlorodimethyl-*iso*-propoxysilane for the enantioselective synthesis of diols **48** *via* addition of the anion of enantiopure hydrazone **45** to the chlorosilane (Scheme 19). Stereocontrolled reduction of the ketone **46**, obtained by ozonolysis of the hydrazone, afforded the silyl alcohols **47a**-*anti* and **47b**-*syn*, unmasking of which led to the diols **48a** and **48b**, respectively, in excellent enantiomeric and diastereomeric excess.

Scheme 19



Carbene addition to silanes is also feasible[88]. For example, α-silyl acetic esters of the type **49** were prepared[78,80c,g] by carbenoid insertion of ethyl diazoacetate into the Si-H bond of Me_2SiClH (Scheme 20), followed by addition of *iso*-propanol and base. Subsequent

Scheme 20



deprotonation using lithium hexamethyldisilazide (LiHMDS) and alkylation with a range of alkyl halides gave access to α-silyl esters of type **50**. Reduction of the ester to the β-hydroxy silane was effected with $LiAlH_4$ to give 1,2-diols **51** after oxidative unmasking.

Reductive hydrosilylation of carbon-carbon double bonds, followed by unmasking, constitutes a useful two-step procedure for the hydration of olefins[53b,c]. The intermolecular version of this reaction is sometimes limited due to low reactivity of the initial

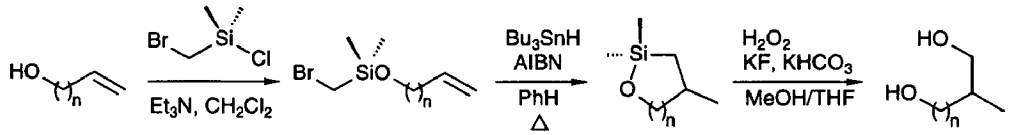
hydrosilylation step. In contrast, the intramolecular reaction[53b,c], *via* tethering of the hydrosilane, was found to be widely applicable since hydration of the double bond proceeds with high regio- and stereoselectivity. In this respect, hydrosilylation provides a useful alternative for the hydroboration reaction.

3.4 Hydroxymethylation

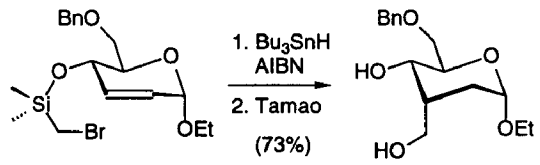
Silyl-based hydroxymethylation can proceed in two ways, *via* radical or nucleophilic addition.

Radical hydroxymethylation is based on silicon tether chemistry. Intermolecular radical couplings often suffer significant by-product formation including homocoupling, polymerization and reduction. Performing a similar reaction intramolecularly, *e.g.* by means of the introduction of a silicon tether, was found to give significantly better results in many cases[23]. An illustrative example is found in radical hydroxymethylation[89] of alkenes (Scheme 21). Silylation of an alcohol (*e.g.* **52**, n=1,2) with the commercially available reagent (bromomethyl)chlorodimethylsilane gave the silyl ether **53** (n=1,2). Alkene **53** could be subjected to radical coupling conditions without further purification to give cyclic **54** (n=1,2), Tamao oxidation of which in the next step led to the corresponding hydroxymethylated product **55** (n=1,2). For instance, the branched sugar **57** was prepared[90] from alkene **56** by such a protocol.

Scheme 21



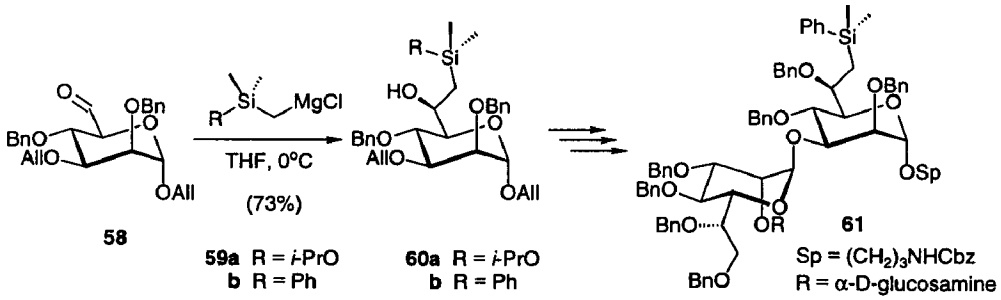
52 **53** **54** **55**



56 **57**

Nucleophilic hydroxymethylation can be executed in a two-step procedure with a variety of reagents. Tamao *et al.* showed[91] that Grignard reagent **59a** (Scheme 22, R=*i*-PrO) underwent condensation with a wide variety of electrophiles, to give, after oxidative unmasking of the silyl moiety, the hydroxymethylated product. The Grignard reagent **59a** was *inter alia* applied in our laboratory[92] in the synthesis of L-*glycero*-D-*manno*-heptopyranose, an essential sugar component of the lipopolysaccharides of Gram-negative

Scheme 22

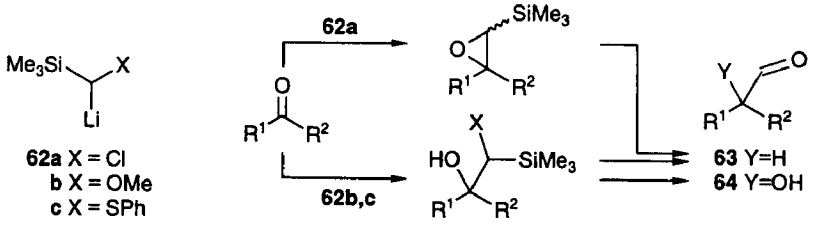


bacteria. Addition of **59a** to aldehyde **58** afforded exclusively the desired *syn*-diastereomer **60a**, oxidative unmasking of which gave the LD-Hep*p* derivative in 64% overall yield. In an improved procedure, the stable phenyl-substituted analogue **59b** was applied[93] in a similar fashion. The β-hydroxy silane adduct **60b** could undergo a variety of synthetic transformations including glycosylation, leading to trisaccharide **61**.

3.5 Formylation

Several silyl-based formyl anion equivalents (Scheme 23), residing on the α-effect and rearrangement reactions of silicon, have been reported. The nucleophilic agents **62a-c**[94], readily obtained *via* α-deprotonation with strong base, react with aldehydes and ketones to afford homologated aldehyde **63**, using **62a**, *via* acid-mediated rearrangement[94a] or, using **62b**, *via* elimination[94b]. On the other hand, the β-hydroxy silanes obtained by addition of **62b** or **62c** can be transformed into α-hydroxy aldehyde **64** by electrochemical oxidation[63] or sila-Pummerer rearrangement[51,94c,d], respectively.

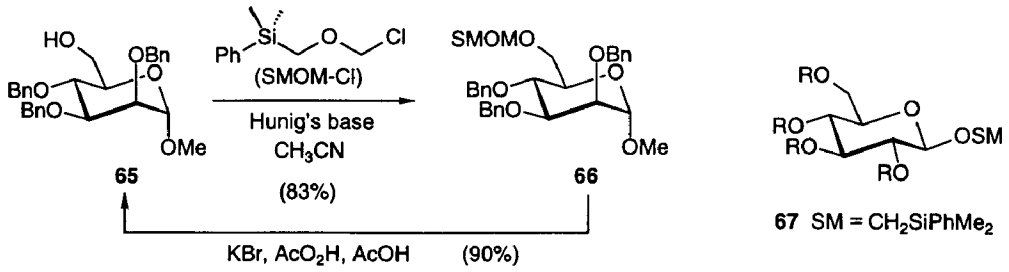
Scheme 23



3.6 Miscellaneous

The silyl moiety as a masked hydroxyl function has found several other applications in organic chemistry. For instance (Scheme 24), the SMOM-group (as in **66**), as well as the SM-protective group (as in **67**) are based on the stability of phenylsilanes against a wide

Scheme 24



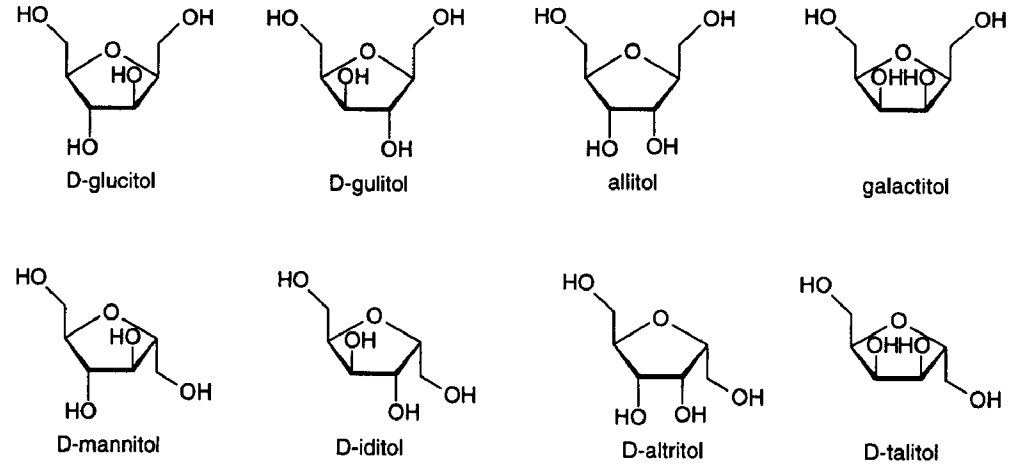
variety of conditions[95]. Deprotection (*e.g.* **66**→**65**) is selectively achieved using one of Fleming's procedures.

4. Outline of the Thesis

This Thesis describes a study towards the silicon-based stereoselective transformation of carbohydrates *en route* to biologically active compounds. Crucial steps involve unique and versatile features of silicon, *e.g.* the β-silicon effect (**Chapter I**) and the oxidative unmasking of the carbon-silicon bond (**Chapters I-VI** and **Chapter VIII**).

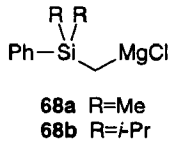
In **Chapter I** and **II**, new approaches towards the synthesis of 2,5-anhydro-hexitols (Figure 3) are presented. The latter compounds are *C*-furanosides, which have found wide application in the synthesis of stable analogues of biologically active compounds.

Figure 3. The 2,5-anhydro-hexitols.

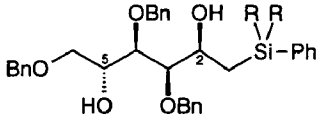


Chapter I[96] deals with the stereoselective synthesis of 2,5-anhydro-hexitols *via* acid-mediated cyclization of 2,5-dihydroxy silanes. For instance (Figure 4), $BF_3{\cdot}Et_2O$ treatment of compound **69a**, obtained by anomeric chain-extension of an arabinose derivative with

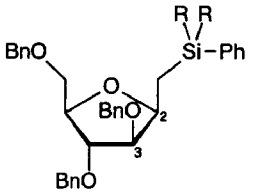
Figure 4



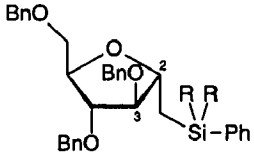
68a R=Me
68b R=*i*-Pr



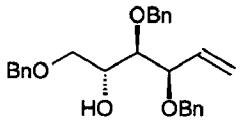
69a R=Me
69b R=*i*-Pr



70a R=Me
70b R=*i*-Pr



71a R=Me
71b R=*i*-Pr

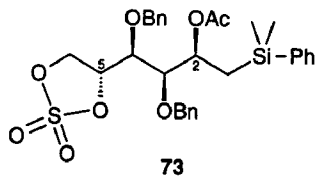


72

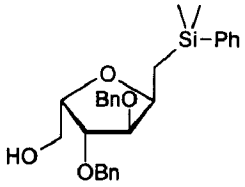
hydroxymethylating reagent **68a**, leads exclusively to 2,3-cis **70a**. On the other hand, H_2SO_4-mediated cyclization of **69a** gives predominantly 2,3-trans product **71a**. The concomitant elimination of **69a** to olefin **72** could be effectively suppressed by enhancing the steric hindrance around silicon. Thus, acid-mediated cyclization of **69b**, obtained by the use of new Grignard reagent **68b**, leads to the exclusive formation of **70b**. The 2,5-anhydro derivatives of D-glucitol, D-mannitol, D-gulitol, D-iditol, allitol and D-altritol could be prepared starting from *arabino*-, *xylo*- and *ribo*-derived 2,5-dihydroxy silanes.

An alternative route towards 2,5-anhydro-hexitols is presented in **Chapter II**[97] and entailed the cyclization of cyclic sulfates of the type **73** (Figure 5). Deacetylation of **73**, prepared *via* addition of hydroxymethylating reagent **68a** to open-chain sugar aldehydes, induced 5-*exo-tet* cyclization to the 5-membered oxacycle **74** *via* intramolecular nucleophilic attack of the deprotected O-2 at C-5 of the cyclic sulfate. A minor quantity of the tetrahydropyran product **75** was also formed. The procedure proved to be successful for the conversion of *arabino*-, *xylo*- and *ribo*-derived cyclic sulfates into 2,5-anhydro-L-iditol, 2,5-anhydro-L-glucitol and 2,5-anhydro-galactitol, respectively. The combined approaches of **Chapter I** and **Chapter II** for the preparation of 2,5-anhydro-hexitols gave access to the complete set depicted in Figure 3.

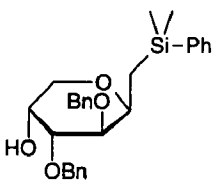
Figure 5



73

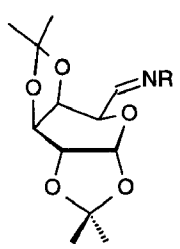


74

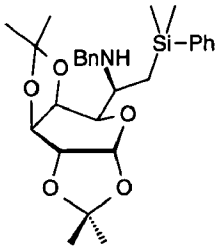


75

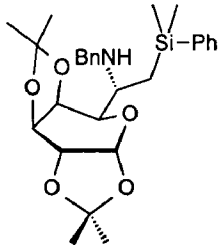
Figure 6



76a R=Ts
76b R=Bn



77

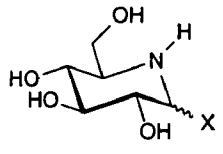


78

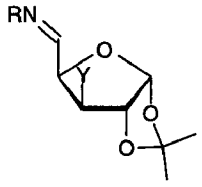
Chapters III-VI deal with hydroxymethylation of carbohydrate imines. In **Chapter III**[98], new procedures for the stereoselective nucleophilic addition of organometallics to imines **76a** and **76b** (Figure 6) are described. It is shown that condensation of Grignard reagent **68a** with tosylimine **76a**, prepared *in situ* from a suitably protected D-galactose aldehyde and *N*-sulfenyl-*p*-toluenesulfonamide, proceeded unsatisfactory in terms of yield and stereoselectivity. On the other hand, nucleophilic addition of **68a** to benzylimine **76b** in the presence of $CeCl_3$ or $CuI/BF_3{\cdot}Et_2O$ showed high diastereofacial selectivity, resulting in the formation of *syn*-adduct **77** and *anti*-adduct **78**, respectively. The latter β-amino silanes proved to be suitable precursors for carbohydrate components of the antibiotics destomycin and lincomycin, respectively.

The latter methodology could also be successfully applied (**Chapter IV**[99]) for the nucleophilic hydroxymethylation of furanose imines. Thus, addition of Grignard **68a** to D-xylo benzylimine **79** (Figure 7) proceeded with high *anti*-selectively in the presence of $CuI/BF_3{\cdot}Et_2O$. On the other hand, cerium(III)-mediated condensation was only feasible starting from organolithium reagent **80**. Similar results were obtained for benzylimines prepared from D-manno and D-galacto furanoses. Further processing of the amino silane adducts gave access to the glucosidase inhibitors nojirimycin (**81a**), mannojirimycin and galactostatin, as well as the 1-deoxy analogues (*e.g.* **81b**).

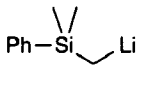
Figure 7



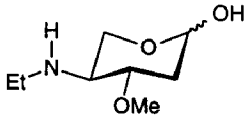
81a X = OH
81b X = H



79 R=Bn, Y=OBn
82 R=Et, Y=H



80



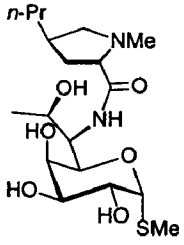
83

The imine hydroxymethylation methodology was further extended, as shown in **Chapter V**[100], in the stereoselective synthesis of 4-ethylamino sugar **83** (Figure 7), a component of the enediyne antibiotic calicheamicin γ_1^I. Cerium(III)-mediated addition of **80** to 3-deoxy

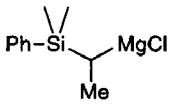
ethylimino sugar **82** resulted in the exclusive formation of the *syn*-diastereomeric adduct, which could be further processed to **83**.

Chapter VI[101] presents a highly straightforward and stereoselective approach towards lincosamine, sugar component of the antibiotic lincomycin (**84**). Nucleophilic addition of the novel α-hydroxyethylating Grignard reagent **85** (Figure 8) to benzylimine **76b** proceeded smoothly in the presence of copper(I) iodide and $BF_3{\cdot}Et_2O$, resulting in the exclusive formation of the 5,6-*anti*/6,7-*anti* adduct **86**. The overall conversion of D-galactose to 6,8-dideoxy-6-amino-D-*erythro*-D-*galacto*octose (*i.e.* lincosamine) *via* this procedure is superior, in terms of yield and number of steps, to earlier reported synthetic approaches.

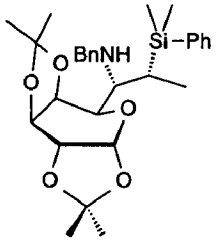
Figure 8



84



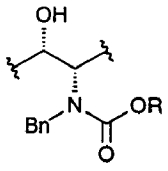
85



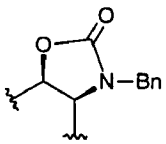
86

The stereoselective synthesis of β-amino alcohols *via* intramolecular nucleophilic susbstitution is described in **Chapter VII**[102]. It will be demonstrated (Figure 9) that treatment of secondary β-hydroxy urethanes of the type **87** (R=Bn or R=Et) with triphenylphosphine and hexachloroethane afforded, with inversion of configuration at the alcoholic carbon, 2-oxazolidinones **88**. The latter compounds could be readily converted into β-amino alcohols by base treatment.

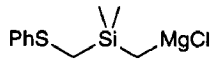
Figure 9



87a R=Bn
87b R=Et



88



89

Chapter VIII[103] deals with a novel silicon-based hydroxymethylating reagent. The easily accessible reagent **89** reacts smoothly with a variety of aldehydes, to give stable β-hydroxy silane adducts. Oxidative demasking of the phenylthiomethylsilyl moiety in the latter adducts using H_2O_2 led to the corresponding diols in excellent yield. Moreover, the reaction rate could be significantly enhanced by the addition of equimolar selenium dioxide.

Acknowledgement We wish to thank Dr. Y. Landais of the 'Université de Lausanne' for sending us a preprint of the Tetrahedron paper on the oxidation of the carbon-silicon bond.

References

1. (a) Fleming, I. *Chem. Soc. Rev.* **1981**, *10*, 83. (b) Weber, W.P. *Silicon Reagents for Organic Synthesis*, Springer-Verlag, Berlin, 1983. (c) Colvin, E.W. *Silicon in Organic Synthesis*, Butterworths, London, 1981; revised edition, Krieger Press, Florida, 1985. (d) Langkopf, E.; Schinzer, D. *Chem. Rev.* **1995**, *95*, 1375.
2. Birchall, J.D. *Chem. Soc. Rev.* **1995**, *24*, 351.
3. Thayer, J.S. *Organometallic Chemistry, An Overview*, VCH publishers, Inc., New York, 1988.
4. (a) Raabe, G.; Michl, J. *Chem. Rev.* **1985**, *85*, 419. (b) Brook, A.G.; Baines, K.M. *Adv. Organomet. Chem.* **1986**, *25*, 1.
5. (a) Walsh, R. *Acc. Chem. Res.* **1981**, *14*, 246. (b) Colvin, E.W. *Silicon Reagents in Organic Synthesis*, Academic Press, London, 1988.
6. Bassindale, A.R.; Taylor, P.G. in *The Chemistry of Organic Silicon Compounds*, Patai, S.; Rappoport, Z., Eds., John Wiley & Sons Ltd, London, 1989, pp. 893.
7. (a) Hathaway, S.J.; Paquette, L.A. *J. Org. Chem.* **1983**, *48*, 3351. (b) Chan, T.H.; Wang, D. *Chem. Rev.* **1992**, *92*, 995.
8. (a) Ushakov, S.N.; Itenberg, A.M. *Zh. Obshch. Khim.* **1937**, *7*, 2495. (b) Jarvie, A.W.P. *Organomet. Chem. Rev. A* **1970**, *6*, 153. (c) Wierschke, S.G.; Chandrasekhar, J.; Jorgensen, W.L. *J. Am. Chem. Soc.* **1985**, *107*, 1496. (d) Lambert, J.B. *Tetrahedron* **1990**, *46*, 2677.
9. Lambert, J.B.; Emblidge, R.W.; Malany, S. *J. Am. Chem. Soc.* **1993**, *115*, 1317.
10. Fleming, I. *Chemtracts* **1993**, 113.
11. (a) Peterson, P.J. *Organomet. Chem. Rev. A* **1972**, *7*, 295. (b) Seyferth, D.; Mammarella, R.E. *J. Organomet. Chem.* **1978**, *156*, 279.
12. Hopkinsen, A.C.; Lien, M.H. *J. Org. Chem.* **1981**, *46*, 998.
13. Chult, C.; Corriu, R.J.P.; Reye, C.; Young, J.C. *Chem. Rev.* **1993**, *93*, 1371.
14. Marat, R.K.; Janzen, A.F. *J. Chem. Soc., Chem. Commun.* **1977**, 671.
15. Kumada, M.; Tamao, K.; Yoshida, J.-I. *J. Organomet. Chem.* **1982**, *239*, 115.
16. Hatanaka, Y.; Hiyama, T. *Synlett* **1991**, 845.
17. Tamao, K.; Hayashi, T.; Ito, Y. *Bull. Chem. Soc. Fr.* **1995**, *132*, 556.
18. (a) Landais, Y.; Jones, G. *Tetrahedron* **1996**, in press. (b) Fleming, I. *Chemtracts* **1996**, in press.
19. (a) Greene, T.W.; Wuts, P.G. *Protective Groups in Organic Synthesis*, 2nd ed., Wiley-Interscience, New York, 1991. (b) Kocieński, P.J. *Protecting Groups*, Georg Thieme Verlag, Stuttgart, 1994.
20. Rücker, C. *Chem. Rev.* **1995**, *95*, 1009.

21. Shimizu, N.; Takesue, N.; Yasuhara, S.; Inazu, T. *Chem. Lett.* **1993**, 1807.
22. Jansson, K.; Ahlfors, S.; Frejd, T.; Kihlberg, J.; Magnusson, G.; Dahmén, J.; Noori, G.; Stenvall, K. *J. Org. Chem.* **1988**, *53*, 5629.
23. Bols, M.; Skrydstrup, T. *Chem. Rev.* **1995**, *95*, 1253.
24. Stork, G.; Kim, G. *J. Am. Chem. Soc.* **1992**, *114*, 1087.
25. (a) Barresi, F.; Hindsgaul, O. *J. Carbohydr. Chem.* **1995**, *14*, 1043. (b) Boons, G.J.P.H. *Tetrahedron* **1996**, *52*, 1095.
26. (a) Xin, Y.C.; Mallet, J.-M.; Sinaÿ, P. *J. Chem. Soc., Chem. Commun.* **1993**, 864. (b) Mallet, A.; Mallet, J.-M.; Sinaÿ, P. *Tetrahedron: Asymmetry* **1994**, *5*, 2593.
27. Rubinstenn, G.; Mallet, A.; Mallet, J.-M.; Sinaÿ, P., poster presented at the *First Euroconference on Carbohydrate Mimics*, Strasbourg, France, May 14-17, **1995**.
28. Hudrlik, P.F.; Peterson, D. *J. Am. Chem. Soc.* **1975**, *97*, 1464.
29. (a) Gilman, H; Tomasi, R.A. *J. Org. Chem.* **1962**, *27*, 3647. (b) Peterson, D.J. *ibid.* **1968**, *33*, 780. (c) Chan, C.H.; Chang, E.; Vinukor, E. *Tetrahedron Lett.* **1970**, 1137.
30. Whitmore, F.C.; Sommer, L.H.; Gold, J.; Van Strien, R.E. *J. Am. Chem. Soc.* **1947**, *69*, 1551.
31. (a) Paquette, L.A. *Science* **1982**, *217*, 793. (b) Cohen, T.; Sherbine, J.P.; Matz, J.R.; Hutchins, R.R.; McHenry, B.M.; Willey, P.R. *J. Am. Chem. Soc.* **1984**, *106*, 3245. (c) Anderson, R. *Synthesis* **1985**, 717. (d) Bellassoued, M.; Ozanne, N. *J. Org. Chem.* **1995**, *60*, 6582.
32. Johnson, C.R.; Tait, B.D. *J. Org. Chem.* **1987**, *52*, 281.
33. Hudrlik, P.F.; Peterson, D. *Tetrahedron Lett.* **1974**, 1133.
34. Hudrlik, P.F.; Peterson, D.; Rona, R.J. *J. Org. Chem.* **1975**, *40*, 2263.
35. Sakurai, H. *Pure & Appl. Chem.* **1982**, *54*, 1.
36. Hosomi, A.; Sakurai, H. *Tetrahedron Lett.* **1976**, 1295.
37. Hosomi, A.; Shirahata, A.; Sakurai, H. *Tetrahedron Lett.* **1978**, 3043.
38. (a) Lewis, M.D.; Cha, J.K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976. (b) Giannis, A.; Sandhoff, K. *Tetrahedron Lett.* **1985**, *26*, 1479.
39. Danishefsky, S.J.; DeNinno, M.P.; Phillips, G.B.; Zelle, R.E.; Lartey, P.A. *Tetrahedron* **1986**, *42*, 2809.
40. Masse, C.E.; Panek, J.S. *Chem. Rev.* **1995**, *95*, 1293.
41. (a) Panek, J.S.; Yang, M.; Xu, F. *J. Org. Chem.* **1992**, *57*, 5790. (b) Panek, J.S.; Cirillo, P.F. *ibid.* **1993**, *58*, 999. (c) Jain, N.F.; Cirillo, P.F.; Pelletier, R.; Panek, J.S. *Tetrahedron Lett.* **1995**, *36*, 8727.
42. (a) Panek, J.S.; Yang, M. *J. Am. Chem. Soc.* **1991**, *113*, 9868. (b) Panek, J.S.; Beresis, R. *J. Org. Chem.* **1993**, *58*, 809.
43. (a) Brook, A.G. *Acc. Chem. Res.* **1974**, *7*, 77. (b) Brook, A.G.; Bassindale, A.R. in *Rearrangements in Ground and Excited States*; de Mayo, P., Ed.; Academic Press, New York, 1980, Vol II.

44. Fleming, I.; Ghosh, S.K. *J. Chem. Soc., Chem. Commun.* **1992**, 1777.
45. (a) Knölker, H.-J.; Jones, P.G.; Pannek, J.-B. *Synlett* **1990**, 429. (b) Imazu, S.; Shimizu, N.; Tsuno, Y. *Chem. Lett.* **1990**, 1845. (c) Snider, B.B.; Zhang, Q. *J. Org. Chem.* **1991**, *56*, 4908. (d) Danheiser, R.L.; Dixon, B.R.; Gleason, R.W. *ibid.* **1992**, *57*, 6094. (e) Ipaktschi, J.; Heydari, A. *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 313. (f) Knölker, H.-J.; Wanzl, G. *Synlett* **1995**, 378 and references cited therein.
46. (a) Eaborn, C. *J. Organomet. Chem.* **1975**, *100*, 43. (b) Bennetau, B.; Dunogues, J. *Synlett* **1993**, 171. (c) Radner, F.; Wistrand, L.-G. *Tetrahedron Lett.* **1995**, *36*, 5093.
47. (a) Wright, A.; West, R. *J. Am. Chem. Soc.* **1974**, *96*, 3214. (b) Wright, A.; West, R. *ibid.* **1974**, *96*, 3227. (c) Linderman, R.J.; Ghannam, A. *ibid.* **1990**, *112*, 2392. (d) Behrens, K.; Kneisel, B.O.; Noltemeyer, M.; Brückner, R. *Liebigs Ann. Chem.* **1995**, 385. (e) Honda, T.; Mori, M. *J. Org. Chem.* **1996**, *61*, 1196.
48. Cai, C.; Vasella, A. *Helv. Chim. Acta* **1995**, *78*, 732.
49. (a) Stork, G.; Colvin, E. *J. Am. Chem. Soc.* **1971**, *93*, 2080. (b) Stork, G.; Ganem, B. *ibid.* **1973**, *95*, 6152. (c) Boeckman Jr., R.K.; Bruza, K.J. *Tetrahedron Lett.* **1974**, 3365.
50. (a) Gilloir, F.; Malacria, M. *Tetrahedron Lett.* **1992**, *33*, 3859. (b) Le Bideau, F.; Aubert, C.; Malacria, M. *ibid.* **1995**, *36*, 697.
51. Brook, A.G.; Anderson, D.G. *Can. J. Chem.* **1968**, *46*, 2115.
52. (a) Ojima, I.; Nagai, Y. *Chem. Lett.* **1973**, 541. (b) Kursanov, D.N.; Parnes, Z.N.; Loim, N.M. *Synthesis* **1974**, 633. (c) Fry, J.L.; Silverman, S.B.; Orfanopoulos, M. *Org. Synth.* **1981**, *60*, 108. (d) Boyer, J.; Corriu, R.J.P.; Perz, R.; Reye, C. *Tetrahedron* **1981**, *37*, 2165. (e) Fujita, M.; Hiyama, T. *J. Am. Chem. Soc.* **1984**, *106*, 4629.
53. (a) Mironov, V.F.; Kozlikov, V.L.; Fedotov, N.S. *Zh. Obshch. Khim.* **1969**, *39*, 937. (b) Tamao, K.; Nakajima, T.; Sumiya, R.; Arai, H.; Higuchi, N; Ito, Y. *J. Am. Chem. Soc.* **1986**, *108*, 6090. (c) Tamao, K.; Tanaka, T.; Nakajima, T.; Sumiya, R.; Arai, H.; Ito, Y. *Tetrahedron Lett.* **1986**, *27*, 3377.
54. (a) Stork, G.; Hudrlik, P.F. *J. Am. Chem. Soc.* **1968**, *90*, 4462. (a) Rasmussen, J.K. *Synthesis* **1980**, 91. (b) Fleming, I. *Chimia* **1980**, *34*, 265. (c) Brownbridge, P. *Synthesis* **1983**, 1.
55. (a) Ainsworth, C.; Kuo, Y.-N.; Chen, J.; Bloomfield, J. *J. Chem. Soc. D* **1971**, 136. (b) Csuk, R.; Schaade, M. *Tetrahedron Lett.* **1993**, *34*, 7907 and references cited therein.
56. Sommer, L.H. *Stereochemistry, Mechanism and Silicon*; McGraw Hill, New York, 1965.
57. (a) Tamao, K.; Ishida, N.; Tanaka, T.; Kumada, M. *Organometallics* **1983**, *2*, 1694. (b) Tamao, K.; Ishida, N. *J. Organomet. Chem.* **1984**, *269*, C37.
58. (a) Fleming, I.; Henning, R.; Plaut, H. *J. Chem. Soc., Chem. Commun.* **1984**, 29. (b) Fleming, I.; Sanderson, P.E.J. *Tetrahedron Lett.* **1987**, *28*, 4229.

59. (a) Tamao, K.; Kakui, T.; Akita, M.; Iwahara, T.; Kanatani, R.; Yoshida, J.; Kumada, M. *Tetrahedron* **1983**, *39*, 983. (b) Tamao, K.; Hayashi, T. in *Frontiers of Organosilicon Chemistry*, Bassindale, R.A. and Gaspar, P.P., Ed. RSC, Cambridge, 1991.
60. Prouilhac-Cros, S.; Babin, P.; Bennetau, B.; Dunoguès, J. *Bull. Soc. Chim. Fr.* **1995**, *132*, 513.
61. (a) Fleming, I.; Henning, R.; Parker, D.C.; Plaut, H.; Sanderson, P.E.J. *J. Chem. Soc., Perkin Trans 1* **1995**, 317. (b) Abd. Rahman, N.; Fleming, I. *J. Chem. Research* **1992**, 292. (c) Fleming, I.; Ghosh, S.K. *J. Chem. Soc., Chem. Commun.* **1992**, 1775.
62. (a) Tamao, K.; Ishida, N. *Tetrahedron Lett.* **1984**, *25*, 4249. (b) Magar, S.S.; Fuchs, P.L. *ibid.* **1991**, *32*, 7513. (c) Magar, S.S.; Desai, R.C.; Fuchs, P.L. *J. Org. Chem.* **1992**, *57*, 5360.
63. (a) Yoshida, J.; Murata, T.; Isoe, S. *J. Organomet. Chem.* **1988**, *345*, C23. (b) Yoshida, J.; Matsunaga, S.; Murata, T.; Isoe, S. *Tetrahedron* **1991**, *47*, 615.
64. (a) Sakurai, H.; Kira, K.; Kumada, M. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 1167. (b) Sato, K.; Kira, M.; Sakurai, H. **1989**, *30*, 4375. (c) Kira, M. *J. Synth. Org. Chem. Jpn.* **1994**, *52*, 510.
65. Tamao, K.; Hayashi, T.; Ito, Y. *Tetrahedron Lett.* **1989**, *30*, 6533.
66. Tamao, K.; Hayashi, T.; Ito, Y. *J. Chem. Soc., Chem. Commun.* **1988**, 795.
67. Bodnar, P.M.; Palmer, W.S.; Shaw, J.T.; Smitrovich, J.H.; Sonnenberg, J.B.; Presley, A.L.; Woerpel, K.A. *J. Am. Chem. Soc.* **1995**, *117*, 10575.
68. Woerpel, K.A., personal communication.
69. Koreeda, M.; Teng, K.; Murata, T. *Tetrahedron Lett.* **1990**, *31*, 5997.
70. Kopping, B.; Chatgilialoglu, C.; Zehnder, M.; Giese, B. *J. Org. Chem.* **1992**, *57*, 3994.
71. Krohn, K.; Khanbabaee, K. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 99.
72. Suginome, M.; Matsunaga, S.; Ito, Y. *Synlett* **1994**, 941.
73. (a) Chan, T.H.; Wang, D. *Tetrahedron Lett.* **1989**, *30*, 3041. (b) Chan, T.H.; Pellon, P. *J. Am. Chem. Soc.* **1989**, *111*, 8737.
74. Taber, D.F.; Yet, L.; Bhamidipati, R.S. *Tetrahedron Lett.* **1995**, *36*, 351.
75. Stork, G. *Pure & Appl. Chem.* **1989**, *61*, 439.
76. Norley, M.C.; Kocieński, P.J.; Faller, A. *Synlett* **1994**, 77.
77. Hunt, J.A.; Roush, W.R. *Tetrahedron Lett.* **1995**, *36*, 501.
78. Landais, Y.; Planchenault, D. *Tetrahedron Lett.* **1995**, *36*, 4565.
79. Angelaud, R.; Landais, Y. *Tetrahedron Lett.* **1995**, *36*, 3861.
80. (a) Palomo, C.; Aizpurua, J.M.; Urchegui, R.; Iturburu, M. *J. Org. Chem.* **1992**, *57*, 1571. (b) Sieburth, S.M.; Fensterbank, L. *ibid.* **1992**, *57*, 5279. (c) Andrey, O.; Landais, Y.; Planchenault, D. *Tetrahedron Lett.* **1993**, *34*, 2927. (d) Winter, E.; Brückner, R. *Synlett* **1994**, 1049. (e) Clive, D.L.J.; Cantin, M. *J. Chem. Soc., Chem.*

Commun. **1995**, 319. (f) Barbero, A.; Cuadrado, P.; Fleming, I.; González, A.M.; Pulido, F.J.; Sanchez, A. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1525. (g) Andrey, O.; Landais, Y.; Planchenault, D. *Tetrahedron* **1995**, *51*, 12083.

81. Fleming, I.; Winter, S.B.D. *Tetrahedron Lett.* **1993**, *34*, 7287.
82. Tamao, K.; Kawachi, A.; Ito, Y. *J. Am. Chem. Soc.* **1992**, *114*, 3989.
83. (a) Benkeser, R.A.; Severson, R.G. *J. Am. Chem. Soc.* **1951**, *73*, 1424. (b) Gilman, H.; Lichtenwalter, G.D. *ibid.* **1958**, *80*, 608. (c) George, M.V.; Peterson, D.J.; Gilman, H. *ibid.* **1960**, *82*, 403.
84. Fleming, I.; Newton, T.W.; Roessler, F. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2527.
85. For a review, see: Tamao, K.; Kawachi, A. *Adv. Organomet. Chem.* **1995**, *38*, 1.
86. Fleming, I. *Pure & Appl. Chem.* **1990**, *62*, 1879.
87. (a) Enders, D.; Nakai, S. *Helv. Chim. Acta* **1990**, *73*, 1833. (b) Enders, D.; Nakai, S. *Chem. Ber.* **1991**, *124*, 219.
88. Bagheri, V.; Doyle, M.P.; Taunton, J.; Claxton, E.E. *J. Org. Chem.* **1988**, *53*, 6158.
89. (a) Nishiyama, H.; Kitajima, T.; Matsumoto, M.; Itoh, K. *J. Org. Chem.* **1984**, *49*, 2298. (b) Stork, G.; Kahn, M. *J. Am. Chem. Soc.* **1985**, *107*, 500. (c) Stork, G.; Sher, P.M. *ibid.* **1986**, *108*, 303. (d) Stork, G.; Sofia, M.J. *ibid.* **1986**, *108*, 6826.
90. Pedretti, V.; Mallet, J.-M.; Sinaÿ, P. *Carbohydr. Res.* **1993**, *244*, 247.
91. (a) Tamao, K.; Ishida, N. *Tetrahedron Lett.* **1984**, *35*, 4245. (b) Tamao, K.; Ishida, N.; Kumada, M. *J. Org. Chem.* **1983**, *48*, 2122.
92. (a) Boons, G.J.P.H.; van der Klein, P.A.M.; van der Marel, G.A.; van Boom, J.H. *Recl. Trav. Chim. Pays-Bas* **1988**, *107*, 507. (b) Boons, G.J.P.H.; van der Marel, G.A.; Poolman, J.T.; van Boom, J.H. *ibid.* **1989**, *108*, 339.
93. (a) Boons, G.J.P.H.; Overhand, M.; van der Marel, G.A.; van Boom, J.H. *Carbohydr. Res.* **1989**, *192*, c1-c4. (b) Boons, G.J.P.H.; van der Marel, G.A.; van Boom, J.H. *Tetrahedron Lett.* **1989**, *30*, 229. (c) Boons, G.J.P.H.; Overhand, M.; van der Marel, G.A.; van Boom, J.H. *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 1504.
94. (a) Burford, C.; Cooke, F.; Ehlinger, E.; Magnus, P. *J. Am. Chem. Soc.* **1977**, *99*, 4536. (b) Magnus, P.; Roy, G. *Organometallics* **1982**, *1*, 553. (c) Kocieński, P.J. *Tetrahedron Lett.* **1980**, *21*, 1559. (d) Ager, D.J.; Cookson, R.C. *ibid.* **1980**, *21*, 1677.
95. Boons, G.J.P.H.; Elie, C.J.J.; van der Marel, G.A.; van Boom, J.H. *Tetrahedron Lett.* **1990**, *31*, 2197.
96. (a) van Delft, F.L.; van der Marel, G.A.; van Boom, J.H. *Tetrahedron Lett.* **1994**, *35*, 1091. (b) van Delft, F.L.; van der Marel, G.A.; van Boom, J.H. *Recl. Trav. Chim. Pays-Bas* **1994**, *113*, 339.
97. van Delft, F.L.; van der Marel, G.A.; van Boom, J.H. *manuscript in preparation.*
98. van Delft, F.L.; de Kort, M.; van der Marel, G.A.; van Boom, J.H. *Tetrahedron: Asymmetry* **1994**, *5*, 2261.

99. van Delft, F.L.; Krempel, R.N.T.C.; de Kort, M.; van der Marel, G.A.; van Boom, J.H. *manuscript in preparation.*
100. van Delft, F.L.; van der Marel, G.A.; van Boom, J.H. *Carbohydr. Lett.* **1996**, *in press.*
101. van Delft, F.L.; de Kort, M.; van der Marel, G.A.; van Boom, J.H. *J. Org. Chem.* **1996**, *61*, 1883.
102. van Delft, F.L.; van der Marel, G.A.; van Boom, J.H. *manuscript in preparation.*
103. van Delft, F.L.; van der Marel, G.A.; van Boom, J.H. *Synlett* **1995**, 1069.

I

Preparation of 2,5-Anhydro-Hexitols (Part I). Silicon-directed Stereocontrolled Cyclization[1]

Abstract

Stereoselective chain-extension of carbohydrate aldehydes with the hydroxymethylating Grignard reagent **1** followed by acid-mediated cyclization gives access to 2,5-anhydro-hexitols. The stereoselectivity of the ring closure depends on the nature of the acid, *i.e.* treatment with excess $BF_3{\cdot}Et_2O$ or catalytic H_2SO_4 leads to tetrahydrofurans with 2,3-cis or 2,3-trans configuration, respectively. Concomitant elimination is effectively suppressed by the introduction of more sterically hindered *iso*-propyl groups on silicon.

Introduction

Earlier results from our laboratory showed[2] (Scheme 1) that nucleophilic addition of the Grignard reagent **1** to 2,3,5-tri-*O*-benzyl-D-arabinose (**2a**) afforded the *syn*-adduct 3,4,6-tri-*O*-benzyl-1-deoxy-1-dimethylphenylsilyl-D-glucitol (**3a**) as a single diastereomer (95% yield). Compound **3a** is prone to elimination[3] due to the β-hydroxy silane moiety in the 1,2-position. Thus, acid-induced ionization at C-2 of **3a** will result in the formation of carbocation **A** or **B** which may afford the terminal olefin **5a**. Alternatively, the cationic intermediates **A** and/or **B** may follow a pathway involving intramolecular nucleophilic attack of the remote C-5 hydroxyl at the cationic center, leading to tetrahydrofuran derivatives **4a** or **6a**. The latter assumption is supported by earlier reports on the formation of 5-membered heterocycles *via* silyl-stabilized carbocations, generated in the course of Lewis-acid mediated allylation of α-substituted aldehydes[4]. Similarly, allylation of

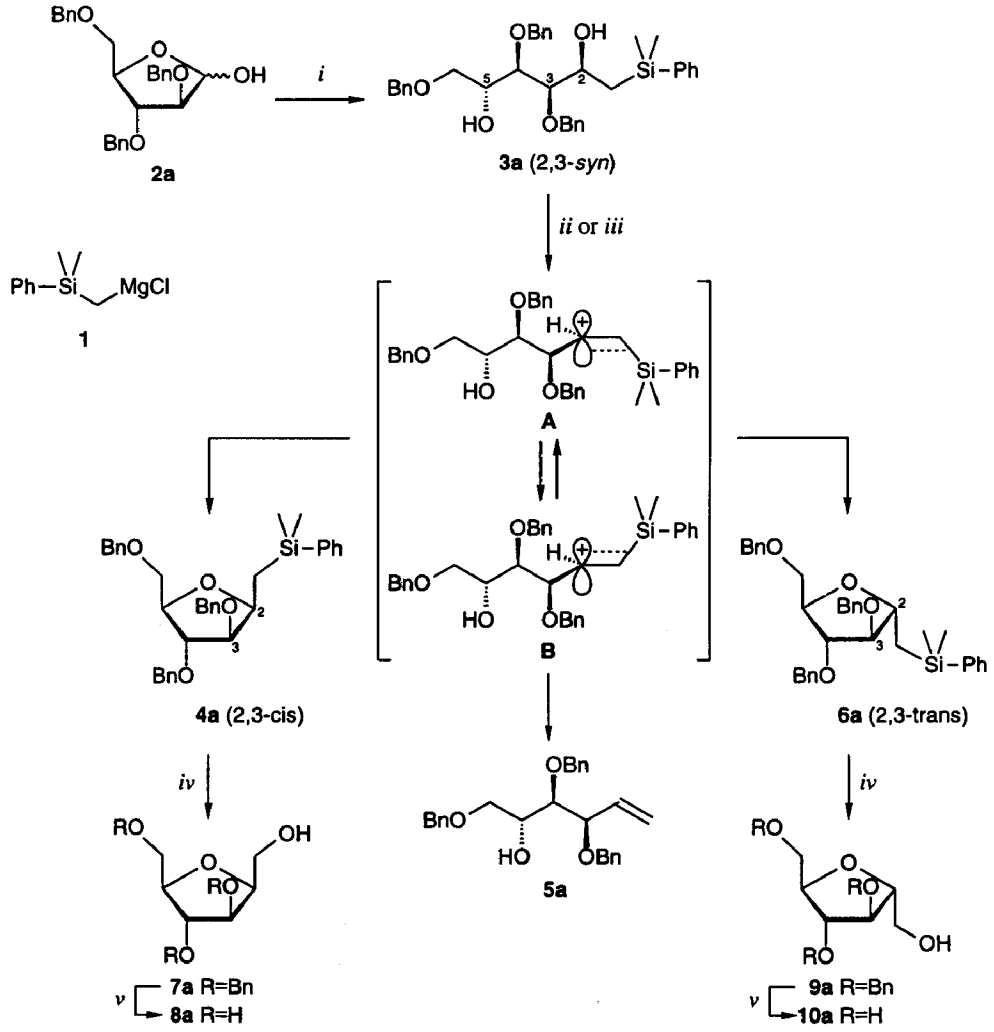
pyruvate esters[5] or addition of (E)-crotylsilanes to aldehydes[6] leads *via* a stereospecific 1,2-silyl shift to the formation of tetrahydrofurans. The latter 1,2-silyl shift also accounts for the formation of cyclopentanes in novel [3+2]-cycloaddition of allylsilanes to α,β-unsaturated ketones[7,8].

In order to verify the possible occurrence of cyclization, silane adduct **3a** (Scheme 1) was treated with a slight excess (1.2 equiv.) of $BF_3{\cdot}Et_2O$ in dichloromethane. TLC-analysis of the reaction mixture, after one hour at 20°C, showed the presence of a minor and a more lipophilic major product. Purification by silica gel chromatography afforded the lower-running compound, the structure of which was in complete accordance with the elimination product **5a**[9] (28%). On the other hand, the ^1H and ^{13}C NMR data of the major product (60% yield) were in agreement with the structure of one of the two possible epimers **4a** or **6a**. The newly introduced stereocenter at C-2 of the cyclic adduct was assigned the *R*-configuration as in stereoisomer **4a** by the following procedure. Unmasking of the silyl function with sodium bromide - peracetic acid[10], and subsequent hydrogenolysis of the benzyl groups of 2,5-anhydro-hexitol **7a** gave homogeneous **8a**, having the same ^1H NMR chemical shifts and optical rotation (*i.e.* $[\alpha]_D$ +23°) as reported[11c] for 2,5-anhydro-D-glucitol. The stereospecific cyclization to the D-*gluco* product **4a** (2,3-cis) can be explained by silicon-directed ionization of the carbon-oxygen bond at C-2 to afford cationic intermediate **A** (Scheme 1). Subsequent kinetically controlled attack of the C-5 hydroxyl *anti* to the C-Si bond in intermediate **A**, in which rotation about the C-C bond is restricted by vertical stabilization[12], leads to the 2,3-cis product **4a**[13].

At this stage we were anxious to find out if the cyclization and concurrent elimination would also occur under the influence of a protic acid. To this end, **3a** was treated with a catalytic amount of H_2SO_4 in THF for 48 h at 60°C. Work-up and purification gave olefin **5a** (50% yield) together with an intractable mixture (45% yield) of two diastereomers (ratio 5:1), the minor component of which was identical with the D-*gluco* silane derivative **4a**. The major cyclization product was assigned the D-*manno* configuration as in 2,3-trans **6a** on the basis of the spectral and chiroptical data of the compounds resulting from a similar sequence of events as for the conversion of **4a** into **8a**. Consequently, unmasking of the silyl group of both diastereomers and separation of the epimers gave homogeneous **9a**. Subsequent hydrogenolysis of **9a** yielded **10a** having the D-*manno* configuration as evidenced by comparison of its spectral data with those of authentic 2,5-anhydro-D-mannitol[11]. The predominant formation of the 2,3-trans derivative **6a** in the H_2SO_4-mediated cyclization of **3a** may be explained by a thermodynamically controlled attack of the C-5 hydroxyl in the inverted cationic intermediate **B**, which has lost its original configurational identity by rotation of the silyl substituent to the position above the plane of the trigonal carbon[14,15].

The scope of the silicon-directed cyclization was further examined for the isomeric D-*ribo* (**2b**)[16] and D-*xylo* (**2c**)[17] furanoses (Scheme 2). Thus, compounds **2b** and **2c** were subjected to excess Grignard reagent **1** (2.5 equiv.) at elevated temperature to give in both

Scheme 1



Reagents and conditions

(*i*) **1**, THF, 60°C, 2 h (95%); (*ii*) $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0°C → rt, 1 h; (*iii*) H_2SO_4, THF, 50°C, 48 h; (*iv*) KBr, AcO_2H, NaOAc, AcOH, 2 h (**7a**: 78%, **9a**: 65%); (*v*) H_2, Pd-C, 5 h (**8a**: 72%, **10a**: 55%).

cases a diastereomeric mixture of *syn*- and *anti*-adducts (*i.e.* **3b** and **3c**, respectively), as gauged by ^{13}C NMR spectroscopy[18]. In order to attain the individual diastereomerically pure adducts **3b** and **3c**, different condensation conditions were explored. However, use of the less polar solvent diethyl ether instead of THF, as well as addition of the organozinc[19] derivative of **1**, resulting from precomplexation with $ZnCl_2$, was abortive.

For this reason, mixtures of the epimeric β-hydroxy silane adducts **3b** (*syn*:*anti* = 4:1) and **3c** (*syn*:*anti* = 5:2) were subjected to acid-mediated cyclization (Table 1). As can be

Table 1. Acid-mediated cyclization of β-hydroxy silanes **3a-c** and **13a-c**.

Entry	Substrate	Cond.[a]	Yields (%) 5	4+6	Ratio[b] 4:6	Entry	Substrate	Cond.[a]	Yields (%) 15	14+16	Ratio[b] 14:16
1	**3a**	A	28	60	1:0	7	**13a**	A	28	53	1:0
2		B	50	45	1:4	8		B	48	43	1:4
3	**3b**[c]	A	58	35	10:3	9	**13b**	A	52	22	1:0
4		B	18	74	2:9	10		B	15	73	1:20
5	**3c**[c]	A	38	50	1:0	11	**13c**	A	35	61	1:0
6		B	60	27	1:2	12		B	61	25	2:3

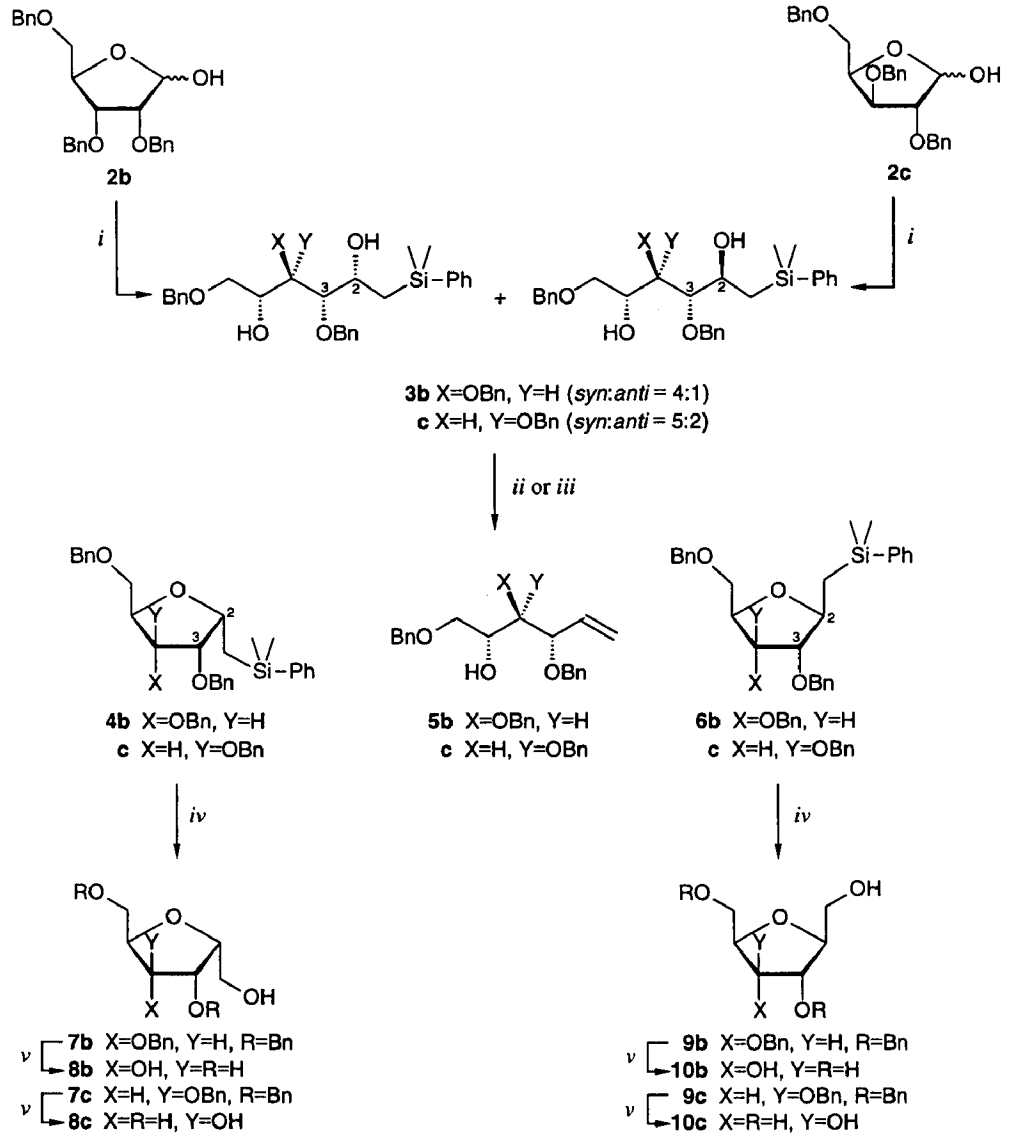
[a]A: $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0°C → rt. B: H_2SO_4, THF, 50°C.
[b]According to ^{13}C NMR spectral analysis.
[c]Mixture of *syn*:*anti* diastereoisomers (**3b**: 4:1, **3c**: 5:2).

seen in entry 3, treatment of **3b** with $BF_3{\cdot}Et_2O$ resulted in the formation of a mixture of 2,5-anhydro-hexitols **4b** (2,3-cis) and **6b** (2,3-trans) in a ratio of 10:3 (35% yield), together with a major amount of elimination product **5b**. In contrast, the *xylose*-derived diastereomers **3c** (entry 5) afforded under the same conditions elimination product **5c** (38%) along with homogeneous 2,3-cis product **4c**. The diastereomeric purity of **4c** suggests that the minor adduct *anti*-**3c** is completely converted into **5b** *via* elimination. The structure of **4b**, **4c** and **6b** was established by their transformation into the known[11] 2,5-anhydro-hexitols of D-altrose (**8b**), D-idose (**8c**) and D-allose (**10b**) according to the same procedure described above for the conversion of **6a** to **10a**[20].

Next, the H_2SO_4-promoted cyclization of the epimeric mixtures of *syn*/*anti* adducts **3b** and **3c** was investigated. Treatment of **3b** affords predominantly the cyclic products **4b** and **6b** together with minor amounts of elimination product **5b** (see entry 4). On the other hand, the major event upon treatment of **3c** with H_2SO_4 (entry 6) was elimination to olefin **5c** (60% yield), with minor cyclization to **4c** and **6c**. In contrast to the $BF_3{\cdot}Et_2O$-mediated reaction, the H_2SO_4-catalyzed cyclization proceeded more sluggishly and showed a preference for the 2,3-trans tetrahydrofuran products **6b** and **6c** (ratio 9:2 and 2:1, respectively). Further processing of **6c** gave 2,5-anhydro-D-gulitol (**10c**), the NMR data of which were identical with those of enantiomeric **9a**[18].

The results thus far obtained show that Grignard addition of **1** to the anomeric center of tribenzylated *arabino*-, *ribo*- and *xylo*-furanoses (**2a-c**) proceeds with a variable degree of *syn*-stereoselectivity. An overall retention of configuration at C-2 occurs preferentially or exclusively in $BF_3{\cdot}Et_2O$-mediated cyclization of the resulting β-hydroxy silane adducts (**3a-c**) to the 2,3-cis tetrahydrofuran derivatives **4a-c**. In contrast, cyclization under the influence of H_2SO_4 shows preference for the 2,3-trans product **6a-c**. However, due to the fact that the β-hydroxy silanes **3b** and **3c** were used as epimeric mixtures, a definite conclusion cannot be drawn at this stage.

Scheme 2



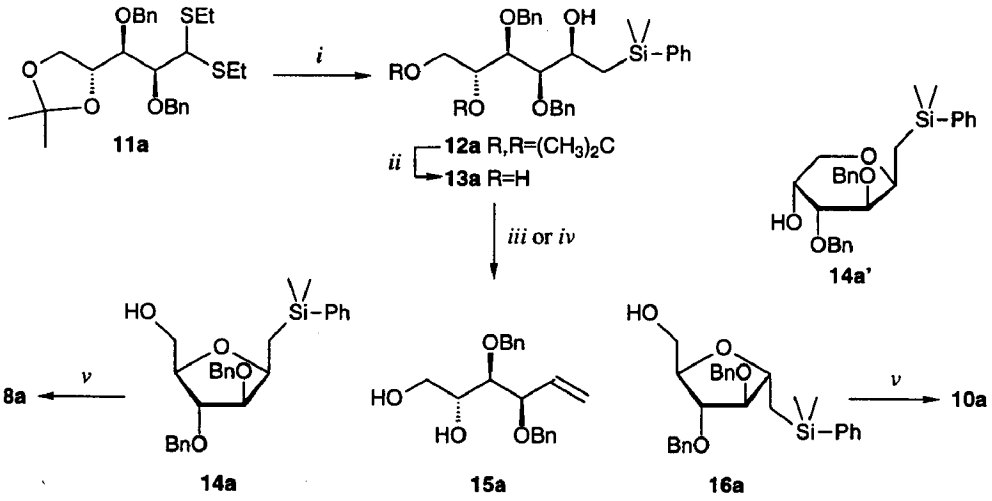
Reagents and conditions

(*i*) **1**, THF, 60°C (**3b**: 87%, **3c**: 66%); (*ii*) $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0°C → rt, 1 h; (*iii*) H_2SO_4, THF, 50°C, 48 h; (*iv*) KBr, AcO_2H, NaOAc, AcOH, 2 h (**7b**: 52%, **7c**: 73%, **9b**: 60%, **9c**: 51%); (*v*) H_2, Pd-C, 5 h (**8b**: 99%, **8c**: 100%, **10b**: 92%, **10c**: 92%).

In order to examine the stereoselectivity of the silicon-directed cyclizations in more detail, attention was focussed on the preparation of diastereomerically pure β-hydroxy silanes. To this end, D-arabinose derived[21] dithioacetal **11a** (Scheme 3) was hydrolyzed

with $HgO/BF_3{\cdot}Et_2O$ in aqueous THF[22]. Treatment of the resulting crude aldehyde in THF with Grignard reagent **1** (0°C) gave a mixture of diastereomeric adducts in a ratio of 5:1, which only slightly improved by executing the condensation at low temperature (-78°C). Fortunately, change of solvent to diethyl ether afforded the diastereomerically pure β-hydroxy silane **12a**, tentatively assigned the 2,3-*syn* configuration, in excellent yield. Next, $BF_3{\cdot}Et_2O$-mediated cyclization of triol **13a**, accessible by hydrolysis of the isopropylidene protective group in **12a**, was examined[23]. As before, starting material **13a** was rapidly transformed (entry 7 in Table 1) into olefin **15a**, along with diastereomerically pure **14a**, the 2,3-cis configuration of which was supported[24] by its conversion into **8a**. Moreover, only a negligible amount of 6-membered cyclic product **14a'** was isolated (1.6%), which confirms[23] the highly preferential formation of the 5-membered ring. Upon treatment of **13a** with H_2SO_4 (entry 8) reversal of stereochemistry occurred, leading to the preferential formation of THF derivative **16a** over **14a** (ratio 4:1) along with elimination product **15a** (48%).

Scheme 3



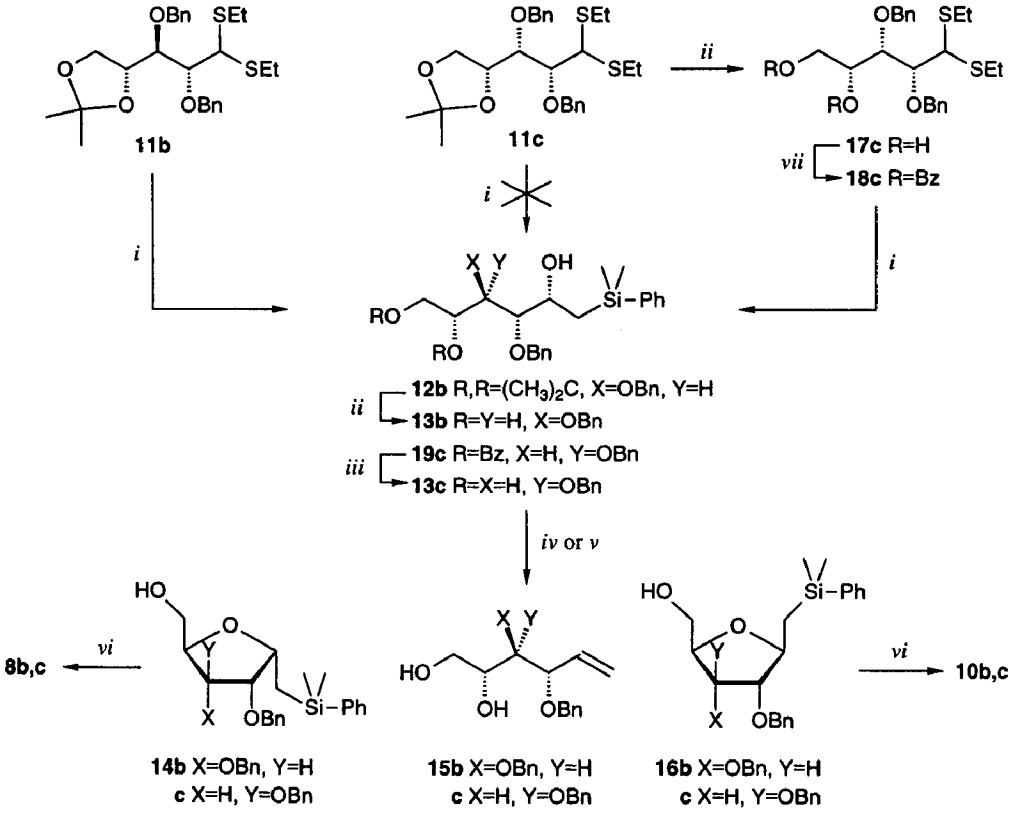
Reagents and conditions

(*i*) (a) HgO, $BF_3{\cdot}Et_2O$, 80% THF, 0.5 h (b) **1**, Et_2O, 0°C, 2 h (90%); (*ii*) 80% AcOH, 16 h (86%); (*iii*) $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0°C → rt, 1 h; (*iv*) H_2SO_4, THF, 50°C; (*v*) (a) KBr, AcO_2H, NaOAc, AcOH, 2 h (b) H_2, Pd-C, 5 h (**8a**: 95%, **10a**: 77%).

At this stage, the cyclization of isomeric triols **13b** and **13c** (Scheme 4) was investigated. Starting from D-ribose and D-xylose dithioacetals **11b** and **11c**, the corresponding triols were prepared following the synthetic route depicted in Scheme 4. Conversion of **11b** into **13b** was effected following the same procedure as described above for **11a**→**13a**. On the other hand, hydrolysis of dithioacetal **11c** with $HgO/BF_3{\cdot}Et_2O$ resulted in the removal of the 4,5-isopropylidene group[25]. For this reason, **11c** was first

transformed into dibenzoylated product **18c** prior to conversion of the thioacetal moiety into the requisite aldehyde function and Grignard addition of **1**. Debenzoylation of the resulting adduct **19c** gave **13c** in good yield. Triols **13b** and **13c** were subjected to $BF_3{\cdot}Et_2O$ or H_2SO_4, the results of which are summarized in Table 1 (entry 9-12). Further processing of the resulting THF-products was executed as described above to give the known[11] 2,5-anhydro-hexitols **8b,c** and **10b,c**.

Scheme 4



Reagents and conditions

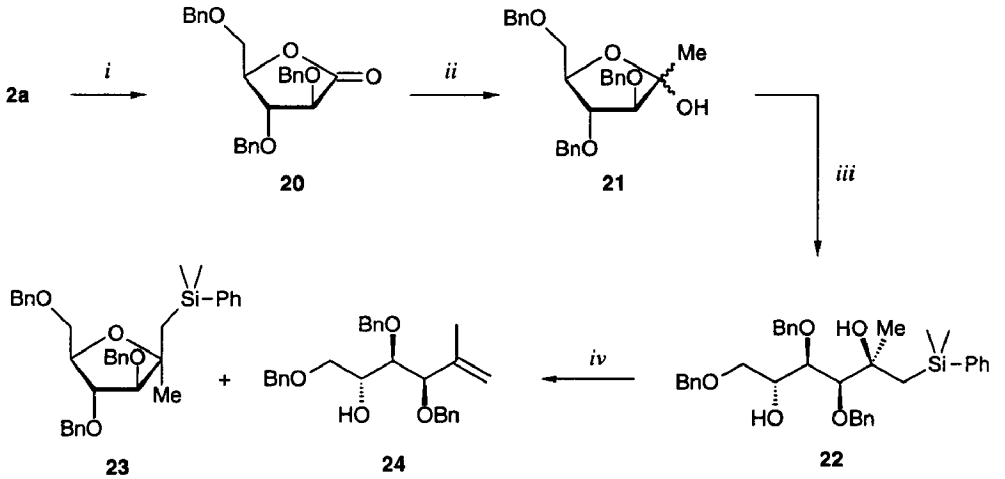
(*i*) (a) HgO, $BF_3{\cdot}Et_2O$, 80% THF, 0.5 h (b) **1**, Et_2O, 0°C, 2 h (**12b**: 67%, **19c**: 71%); (*ii*) 80% AcOH, 16 h (**13b**: 92%, **17c**: 87%); (*iii*) BzCl, pyridine, 20 h (93%); (*iv*) KO*t*-Bu, MeOH (87%); (*v*) $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0°C → rt, 1 h; (*vi*) H_2SO_4, THF, 50°C; (*vii*) (a) KBr, AcO_2H, NaOAc, AcOH, 2 h (b) H_2, Pd-C, 5 h (**8b**: 90%, **8c**: 93%, **10b**: 77%, **10c**: 97%).

In summary, the stereochemistry of the cyclization of β-hydroxy silanes, having a hydroxyl function at C-5 (*i.e.* **3a-c**), or a 5,6-diol moiety (*i.e.* **13a-c**) to the corresponding tetrahydrofuran derivatives can be directed by choice of acid. In this respect, the stereospecific cyclization under the influence of $BF_3{\cdot}Et_2O$, *i.e.* with retention of

configuration at C-2, seems particularly advantageous.

The scope of the $BF_3 \cdot Et_2O$-mediated cyclization was further evaluated with the tertiairy alcohol **22** as a substrate (Scheme 5). To this end, known[26] D-*arabinono* lactone **20**, readily accessible by oxidation of **2a** with DMSO and Ac_2O, was monomethylated (MeLi, -78°C), followed by condensation of the resulting ketosugar **21** with Grignard reagent **1** at elevated temperature. The configuration of the stereogenic center at C-2 of the resulting homogeneous β-hydroxy silane adduct **22** was tentatively assigned the 2,3-*syn* configuration. Treatment of diol **22** with $BF_3 \cdot Et_2O$ gave THF derivative **23** and elimination product **24**, in a yield of 24% and 64%, respectively. The preference of **22** to eliminate to compound **24** may be explained by the formation of a more highly substituted alkene. The 2,3-cis configuration of the diastereomerically pure product **23** was irrefutably established by nOe experiments, indicating that cyclization also in this case occurred with retention of configuration at C-2.

Scheme 5



Reagents and conditions

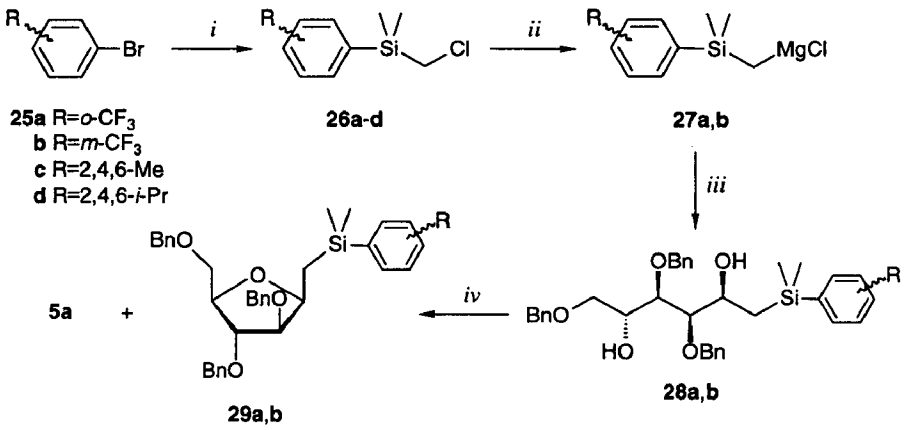
(*i*) DMSO, Ac_2O, 16 h (92%); (*ii*) MeLi, THF, -78°C (94%); (*iii*) **1**, THF, 60°C (71%); (*iv*) $BF_3 \cdot Et_2O$, CH_2Cl_2, 0°C → rt, 1 h (**23**: 24%, **24**: 64%).

In order to increase the value of the silicon-directed cyclization towards the synthesis of 2,5-anhydro-hexitol containing compounds two strategies to prevent the acid-induced elimination of the β-hydroxy silanes were examined. It was anticipated that an electron-withdrawing group at the phenyl substituent at silicon would stabilize the carbon-silicon bond[27]. Alternatively, we envisaged that elimination could be suppressed by the introduction of more steric congestion around silicon[28].

The preparation of organosilanes **27a** and **27b** containing an electron-withdrawing group at the phenyl ring is depicted in Scheme 6. Metal-halogen exchange of *ortho*- and *meta*-

CF_3-phenyl bromides **25a** and **25b** with *n*-BuLi and subsequent reaction with commercially available chloro(chloromethyl)dimethylsilane afforded chlorides **26a** and **26b**, respectively. In the next step, D-*arabino* furanose derivative **2a** was treated with Grignard reagents **27a** and **27b**, prepared in turn by metallation of the individual chlorides **26a** and **26b** with magnesium, to give the respective *syn*-adducts **28a** (R=*o*-CF_3) and **28b** (R=*m*-CF_3). The $BF_3{\cdot}Et_2O$-mediated cyclization of **28a** and **28b** proceeded sluggishly[29] (reaction was complete after 6 h and 4.5 h at 20°C, respectively). Apart from the expected D-glucitol derivatives **29a** (R=*o*-CF_3, 54%) and **29b** (R=*m*-CF_3, 58%) a substantial amount of the undesired elimination product **5a** (27 and 43%, respectively) was formed. The latter results show that the introduction of more electronegative groups in the organosilane does not exert a beneficial effect on the cyclization/elimination ratio.

Scheme 6



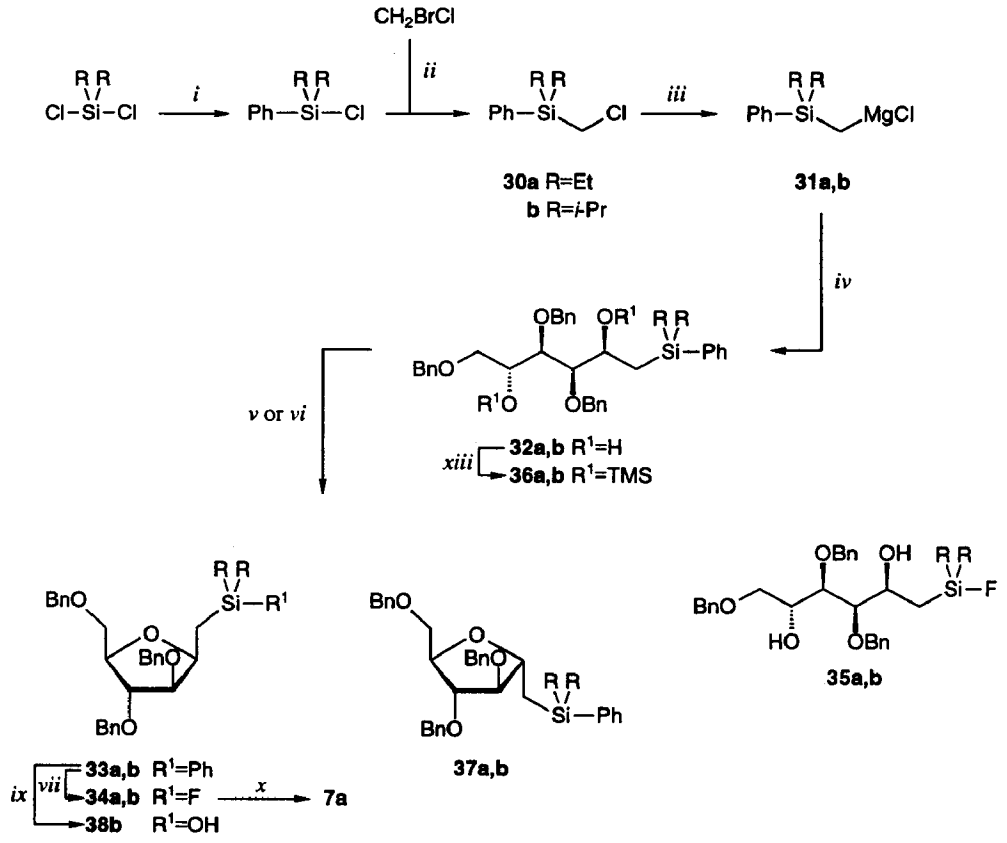
Reagents and conditions

(*i*) (a) *n*-BuLi, Et_2O, 0°C, 1 h (b) $ClSi(CH_3)_2CH_2Cl$, 0°C (**26a**: 88%, **26b**: 83%); (*ii*) Mg, THF, reflux; (*iii*) **2a**, THF, 60°C, 2 h (**28a**: 73%, **28b**: 97%); (*iv*) $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0°C → rt.

The influence of sterically congested substituents at the phenyl moiety on the cyclization process may be explored using the reagents **26c** and **26d** (Scheme 6). Unfortunately, addition of the lithiated derivatives of mesitylbromide (**25c**)[30] or tri-*iso*-propylphenylbromide (**25d**)[31], to chloro(chloromethyl)dimethylsilane was abortive. Therefore, attention was focussed on the synthesis of the derivatives **32a** and **32b** (Scheme 7), having the bulky ethyl and *iso*-propyl groups at silicon. Diastereomerically pure derivatives **32a** (R=Et) and **32b** (R=*i*-Pr) could be isolated in excellent yield by chain extension of **2a** with the Grignard reagents **31a** (R=Et) and **31b** (R=*i*-Pr). The requisite chlorides **30a** and **30b** were prepared by sequential monophenylation and addition of chloromethyllithium[32] to the corresponding dichlorodialkylsilanes.

The results of the acid-mediated cyclization of **32a,b** are summarized in Table 2. First of all, it was found (entry 1,4) that elimination of **32a** is effectively diminished, *i.e.* olefin **5a** is isolated in only 12% yield from **32a** (R=Et) whereas no trace of elimination was observed in case of **32b**. However, analysis of the reaction products revealed, apart from the expected 2,5-anhydro-D-glucitol derivatives (*i.e.* **33a** and **33b**), the presence of fluorosilanes **34a,b** (R^1=F) and **35a,b**, the structures of which were corroborated by independent synthesis. Thus, treatment of **33a** and **33b** with acetic acid in the presence of $BF_3{\cdot}Et_2O$[33] yielded the corresponding fluorosilanes **34a** and **34b**, as indicated by ^{13}C NMR spectroscopy. The structure of the minor open-chain fluorosilanes **35a** and **35b**, resulting from protodesilylation of the phenyl group in **32a** and **32b**, was also evidenced by NMR spectroscopy and mass spectrometry.

Scheme 7



Reagents and conditions

(*i*) PhLi, Et_2O, -78°C, 0.5 h; (*ii*) *n*-BuLi, THF, -65°C (**30a**: 36%, **30b**: 72%); (*iii*) Mg, THF, reflux; (*iv*) **2a**, THF, 60°C, 2 h (**32a**: 85%, **32b**: 88%); (*v*) $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0°C → rt; (*vi*) H_2SO_4, THF, 50°C, 48 h; (*vii*) $BF_3{\cdot}Et_2O$, AcOH, CH_2Cl_2 (**34a**: 86%; **34b**: 94%); (*xiii*) HMDS, TMSCl, MeCN; (*ix*) KBr, AcO_2H, NaOAc, AcOH (**38a**: 40%; **38b**: 53%); (*x*) *t*-BuOOH, CsOH, DMF, 70°C, 4 h (71% from **33b**).

Table 2. Influence of the silyl substituent R on the cyclization/elimination ratio of **32**.

Entry	Substrate	Conditions[a]	Time (h)	Yields (%) 5a	33	34	35	37
1	**32a** (R=Et)	A	1	12	53	11	5	0
2		B	1	7	83	0	0	0
3		C	72	15	28(38)[b]	0	0	28(38)[b]
4	**32b** (R=*i*-Pr)	A	0.75	0	37	30	14	0
5		B	0.75	0	90	0	0	0
6		C	72	0	33(62)[b]	0	0	7(13)[b]

[a]A: $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0 → rt. B: (a) HMDS, TMSCl, CH_3CN (b) $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0°C → rt. C: H_2SO_4, THF, 50°C.
[b]Based on recovered starting material (**32a**: 27%, **32b**: 47%).

It occurred to us that the undesired protodesilylation could be prevented by prior silylation of the hydroxyl groups in **32a,b**. Indeed, $BF_3{\cdot}Et_2O$-assisted ring-closure of fully silylated **36a** (entry 2), resulting from reaction of **32a** with hexamethyldisilazane and catalytic trimethylsilyl chloride in acetonitrile, afforded 2,5-anhydro-D-glucitol derivative **33a** (R=Et, 83% yield) without formation of fluorosilanes **34a** and **35a**. The same holds for cyclization of **36b** with $BF_3{\cdot}Et_2O$ (entry 5), leading to the exclusive formation of **33b** (R=*i*-Pr) in excellent yield (90%).

A substantial decrease of elimination was also observed upon cyclization of **32a** and **32b** under the agency of catalytic H_2SO_4 (entry 3,6), resulting in intractable mixtures of the two 2,5-anhydro diastereoisomers **33** and **37** (R=Et: 1:1, R=*i*-Pr: 5:1). At the same time, however, the rate of intramolecular reaction was significantly decreased, *e.g.* nearly half of starting material **32b** was recovered after 72 h at 60°C (*cf.* H_2SO_4-mediated cyclization of **2a** went to completion within 48 h). These results indicate that the efficacy of the formation of the 2,5-anhydro-D-mannitol derivative is inversedly correlated to the bulkiness of the silyl moiety. The latter effect might be explained by encumbered rotation around the carbon-carbon bond in the initially formed silyl-stabilized carbocation **A** (Scheme 1).

Oxidative unmasking of tetrahydrofuran **33b** under Fleming conditions[10], *i.e.* treatment with KBr in peracetic acid, resulted in silanol **38b** instead of the desired alcohol **7a**. Likewise, Tamao oxidation[34] of the fluorosilane **34b** with H_2O_2 and KF in THF/MeOH led to exclusive formation of **38b** (54%). These results suggest that rearrangement of the respective peracetoxysilyl or perhydroxysilyl intermediates (see General Introduction) is hampered by the sterically demanding *iso*-propyl groups[35]. Very recently, it was reported by Woerpel *et al.*[36] that oxidation of a carbon-silicon bond in sterically congested alkoxysilanes can be realized with *tert*-butyl hydroperoxide, cesium fluoride and

tetrabutylammonium fluoride (TBAF) at elevated temperature. It was anticipated that under these conditions a fluorosilane is formed *in situ*. Therefore, fluorosilane **34b** was subjected to the *tert*-butyl hydroperoxide conditions in the absence of TBAF. After 4 h at 70°C, **34b** was completely converted into a single product (71% yield), which was in all aspects identical with previously prepared **7a**.

Conclusion

The results described in this paper indicate that the two-step approach comprising hydroxymethylation of sugar aldehydes, followed by acid-mediated cyclization of the resulting adducts, may present a valuable asset in the preparation of 2,5-disubstituted tetrahydrofurans[37]. Both hydroxymethylation and cyclization are under high stereocontrol and elimination to the olefin may be completely suppressed by the introduction of sterically hindered substituents at silicon. Final oxidative unmasking using the novel conditions designed by Woerpel gives the resulting 2,5-anhydro-hexitols, which are valuable starting compounds for the synthesis of biologically important C-glycosides[38].

Acknowledgement We wish to thank dr. I. Fleming for his critical remarks.

Experimental

General methods and materials - Toluene was distilled from P_2O_5 and stored over 4Å molecular sieves, tetrahydrofuran and diethyl ether were freshly distilled from $LiAlH_4$ and dried over 4Å molecular sieves for one hour. Methanol (HPLC-grade, Rathburn), 1,4-dioxane and acetic acid were used as received. All reactions were performed under strictly anhydrous conditions unless noted otherwise. Reactions were followed by TLC analysis on Schleicher and Schüll DC Fertigfolien F 1500 LS 254. Compounds were visualized by UV light (254 nm) and by spraying with 20% sulfuric acid in methanol followed by charring at 140°C. Column chromatography was performed on silicagel 60, 230-400 mesh (Merck). ^1H NMR spectra and ^{13}C NMR spectra (50.1 MHz) were recorded in $CDCl_3$ using a Jeol JNM-FX 200 spectrometer, unless noted otherwise. ^1H NMR spectra (300 MHz) were recorded using a Bruker WM-300 spectrometer. Chemical shifts (δ) are given in ppm relative to tetramethylsilane as internal standard. Optical rotations were measured in $CHCl_3$ on a Propol automatic polarimeter. Mass spectra were recorded on a Finnigan MAT TSQ70 triple quadrupole mass spectrometer. (Chloromethyl)dimethylphenylsilane was obtained from Aldrich Chemical Co. and used as received.

[Dimethylphenylsilyl]methylmagnesium chloride (1), 1M in THF or Et_2O - Under a N_2-atmosphere magnesium powder (0.56 g, 23.1 mmol) in refluxing solvent (THF or Et_2O, 3 mL) was activated by the addition of 1,2-dibromoethane (0.1 mL). Next, (chloromethyl)dimethylphenylsilane (3.79 mL, 21.0 mmol) in the same solvent (15 mL) was slowly added at such a rate as to maintain a gentle reflux. After the addition was complete, the resulting dark-grey mixture was stirred an additional hour at 40°C (THF) or 30°C (Et_2O).

General procedure for Grignard addition of 1 to furanoses 2a-c - Compound **2** (1 mmol) was dissolved in THF (5 mL) and cooled to 0°C. A solution of **1** in THF (3 mL, 1 M) was added *via* syringe and the reaction mixture was heated to 60°C. After TLC analysis indicated the complete disappearance of **2**, the mixture was cooled to 0°C, quenched by the addition of aqueous NH_4Cl (10 mL, 20%) and extracted with Et_2O (50 mL). The organic layer was washed with H_2O (30 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The oil thus obtained was purified by column chromatography.

3,4,6-Tri-*O*-benzyl-1-deoxy-1-dimethylphenylsilyl-D-glucitol (3a) - Compound **2a**[16] (2.94 g, 7 mmol) was treated with **1** according to the general procedure. The oil obtained after extraction was applied onto a column of silica gel and elution was effected with Et_2O/light petroleum (1/2→1/1, v/v) to afford **3a** as an oil. Yield 3.79 g (95%). R_f 0.6 (toluene/EtOAc, 3/2, v/v). $[\alpha]_D^{20}$ -6.1 (c 3). ^1H NMR: δ 7.52-7.16 (m, 20H, H-arom), 4.59 (AB, 2H, CH_2, Bn, *J* -11.3 Hz), 4.51, 4.50 (2x s, 4H, CH_2, Bn), 4.12-3.96 (m, 2H, H-2, H-5), 3.71-3.60 (m, 3H, H-4, H-6), 3.45 (t, 1H, H-3), 2.90 (d, 1H, OH, *J* 5.6 Hz), 2.51 (d, 1H, OH, *J* 7.3 Hz), 1.13 (dd, 1H, H-1a, $J_{1a,1b}$ -14.6 Hz, $J_{1a,2}$ 9.9 Hz), 0.98 (dd, 1H, H-1b, $J_{1b,2}$ 4.5 Hz), 0.30, 0.34 (2x s, 6H, $SiCH_3$). $^{13}C\{^1H\}$ NMR: δ 139.2, 137.9, 137.7 (Cq, arom), 133.3-127.4 (CH, arom), 83.9, 78.1 (C-3, C-4), 74.4, 73.3, 73.0 (CH_2, Bn), 71.0 (C-6), 70.5, 68.4 (C-2, C-5), 21.6 (C-1), -1.9, -2.7 ($SiCH_3$).

General procedure for BF_3·Et_2O-mediated cyclization - To an ice-cooled solution of a β,ε-dihydroxy silane (1.0 mmol) in CH_2Cl_2 (10 mL) was quickly added $BF_3.Et_2O$ (0.14 mL, 1.1 mmol) and the mixture was allowed to reach rt. After TLC analysis indicated the disappearance of starting material, Et_3N (0.21 mL, 1.5 mmol) was added. The mixture was diluted with CH_2Cl_2 (30 mL), washed with H_2O (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel.

BF_3·Et_2O-mediated cyclization of 3a - Diol **3a** (0.72 g, 1.26 mmol) was treated with BF_3·Et_2O as described above to give two products (R_f 0.5 and R_f 0.8) as indicated by TLC analysis (Et_2O/light petroleum, 3/1, v/v). The oil obtained after work-up was applied onto a column of silica gel, which was eluted with Et_2O/light petroleum (1/4→1/3, v/v) to give 2,5-anhydro-3,4,6-tri-*O*-benzyl-1-deoxy-1-dimethylphenylsilyl-D-glucitol (**4a**). Yield 0.42 g (60%). R_f 0.8 (Et_2O/light petroleum, 1/1, v/v). $[\alpha]_D^{20}$ -9.0 (c 2). MS (m/z): 571 $[M+H]^+$. ^1H NMR: δ 7.55-7.18 (m, 20H, H-arom), 4.52 (AB, 2H, CH_2, Bn, *J* -12.0 Hz), 4.47 (AB, 2H, CH_2, Bn, *J* -12.1 Hz), 4.24 (AB, 2H, CH_2, Bn, *J* -11.8 Hz), 4.10 (ddd, 1H, H-2, $J_{1a,2}$ 6.9 Hz, $J_{1b,2}$ 8.0 Hz, $J_{2,3}$ 3.5 Hz), 3.97 (ddd, 1H, H-5, $J_{4,5}$ 3.2 Hz, $J_{5,6a}$ 5.9 Hz, $J_{5,6b}$ 6.4 Hz), 3.85 (dd, 1H, H-4, $J_{3,4}$ 0.7 Hz), 3.59 (dd, 1H, H-6a, $J_{6a,6b}$ -9.9 Hz), 3.54 (dd, 1H, H-3), 3.49 (dd, 1H, H-6b), 1.36 (dd, 1H, H-1a, $J_{1a,1b}$ -14.3 Hz), 1.28 (dd, 1H, H-1b), 0.31, 0.29 (2x s, 6H, $SiCH_3$). $^{13}C\{^1H\}$ NMR: δ 139.2, 138.8, 138.6, 138.5 (Cq, arom), 134.1-127.9 (CH, arom), 84.7, 84.3, 82.7, 79.6 (C-2, C-3, C-4, C-5), 73.6, 71.9, 71.3, 71.2 (CH_2, Bn, C-6), 16.1 (C-1), -1.5, -2.0 ($SiCH_3$). Further elution gave 3,4,6-tri-*O*-benzyl-1,2-dideoxy-D-*arabino*-hex-1-enitol (**5a**). Yield 0.15 g (28%). R_f 0.5 (Et_2O/light petroleum, 3/1, v/v). $[\alpha]_D^{20}$ +4.8 (c 1)(Lit.[9] +4.6). ^1H NMR: δ 7.35-7.24 (m, 15H, H-arom), 5.97 (ddd, 1H, H-2, $J_{1a,2}$ 11.3 Hz, $J_{1b,2}$ 16.5 Hz, $J_{2,3}$ 7.5 Hz), 5.33 (m, 2H, H-1), 4.59 (AB, 2H, CH_2, Bn, *J* -11.5 Hz), 4.50 (s, 2H, CH_2, Bn), 4.49 (AB, 2H, CH_2, Bn, *J* -12.0 Hz), 4.09 (dd, 1H, H-3, $J_{3,4}$ 4.0 Hz), 4.03 (m, 1H, H-5), 3.64 (dd, 1H, H-4, $J_{4,5}$ 7.0 Hz), 3.61 (d, 2H, H-6, $J_{5,6}$ 4.0 Hz), 2.84 (d, 1H, OH, *J* 5.0 Hz). $^{13}C\{^1H\}$ NMR: δ 138.0, 137.9, 137.7 (Cq, arom), 135.0 (C-2), 128.3-127.5 (CH, arom), 118.8 (C-1), 80.5, 80.1 (C-3, C-4), 74.0, 73.2, 70.8, 70.5 (CH_2, Bn, C-6), 70.3 (C-5).

General procedure for oxidative unmasking of phenylsilanes with KBr and AcO_2H - NaOAc (1.07 g, 13.0 mmol) was dissolved, with heating, in AcOH (10 mL) and the solution was added to a phenylsilane (1.0 mmol). KBr (0.14 g, 1.20 mmol) was added, the mixture was cooled to 10°C, and AcOOH (5.0 mL, 30% in AcOH) was added dropwise under exclusion of light. During the addition gas was liberated. The reaction mixture was stirred until TLC analysis indicated complete conversion of the starting material into a more hydrophilic product. The mixture was diluted with EtOAc (50 mL) and poured into a cooled (0°C) solution of $Na_2S_2O_3$ (10 mL, 15%). The layers were separated and to the organic phase was added a saturated solution of $NaHCO_3$ (15 mL), followed by solid $NaHCO_3$ until no more gas evolved. The organic phase was washed with H_2O (15 mL), dried ($MgSO_4$), filtered and concentrated. The residue was coevaporated with toluene (2x 5 mL) and purified by silica gel column chromatography.

2,5-Anhydro-3,4,6-tri-*O*-benzyl-D-glucitol (7a) - Compound **4a** (0.18 g, 0.32 mmol) was oxidatively unmasked as described in the general procedure to give **7a** as an oil. Yield 0.11 g (78%). R_f 0.2 (Et_2O/light petroleum, 1/1, v/v). $[\alpha]_D^{20}$ -26.4 (c 1). ^1H NMR: δ 7.35-7.22 (m, 15H, H-arom), 4.55 (2x s, 2H, CH_2, Bn), 4.48 (AB, 2H, CH_2, Bn, J -11.8 Hz), 4.11-3.83 (m, 6H, H-1, H-2, H-3, H-4, H-5), 3.60 (d, 2H, H-6, $J_{5,6}$ 5.1 Hz), 2.35 (s, 1H, OH). $^{13}C\{^1H\}$ NMR: δ 137.7, 137.6, 137.4 (Cq, arom), 128.4-127.5 (CH, arom), 83.6, 83.0, 81.7, 80.2 (C-2, C-3, C-4, C-5), 73.2, 71.7, 70.0 (CH_2, Bn, C-6), 61.5 (C-1).

General procedure for hydrogenolysis - To a degassed solution of a benzylated compound (1 mmol) in MeOH (5 mL) was added 10% Pd-C (0.2 g). After applying a brief vacuum, a H_2-atmosphere was introduced and the mixture was stirred at 20°C until TLC-analysis indicated the complete disappearance of UV-positive products. The catalyst was removed by filtration over Hyflo and rinsing with MeOH. Evaporation of solvent afforded the crude product.

2,5-Anhydro-D-glucitol (8a) - Alcohol **7a** (0.11 g, 0.25 mmol) was hydrogenated for 24 h as described in the general procedure to give **8a** as an amorphous material, which crystallized when scratched. Yield 30 mg (72%). R_f 0.2 (EtOAc/MeOH, 85/15, v/v). Mp 54-56°C (Lit.[11c] 56-57°C). ^1H NMR: Table 3. $^{13}C\{^1H\}$ NMR (H_2O): δ 85.0 (C-5), 81.4 (C-2), 78.4 (C-4), 77.3 (C-3), 62.1 (C-6), 60.6 (C-1).

General procedure for H_2SO_4-mediated cyclization - To a solution of a silane (1 mmol) in THF (5 mL) was added 1 drop of concentrated H_2SO_4. The solution was heated to 50°C and stirred until TLC-analysis indicated complete disappearance of starting material. The mixture was cooled to rt and partitioned between Et_2O (20 mL) and $NaHCO_3$ (5 mL, 15%). The layers were separated and the organic layer was dried ($MgSO_4$), filtered and concentrated, followed by purification by flash chromatography.

*H_2SO_4-mediated cyclization of **3a*** - Cyclization of **3a** (0.70 g, 1.23 mmol) in the presence of H_2SO_4 was performed as described above to afford, after work-up and silica gel chromatography 2,5-anhydro-3,4,6-tri-*O*-benzyl-1-deoxy-1-dimethylphenylsilyl-D-mannitol (**6a**) and **4a** as an intractable 4:1 mixture. Yield 0.31 g (45%). R_f 0.8 (Et_2O/light petroleum, 3/1, v/v). Compound **6a**: $^{13}C\{^1H\}$ NMR: δ 139.2, 138.8, 138.5 (Cq, arom), 133.5-127.4 (CH, arom), 89.5, 85.4, 80.9, 80.2 (C-2, C-3, C-4, C-5), 73.1, 71.5, 71.3, 70.4 (CH_2, Bn, C-6), 20.9 (C-1), -1.5, -2.0 ($SiCH_3$). Futher elution gave olefin **5a**. Yield 0.26 g (50%).

Table 3. Optical rotation and measured ^{1}H NMR data (300 MHz) of 2,5-anhydro-hexitols[a]

Compound (2,5-anhydro-)	[α] (H_2O)	H-1a ($J_{1a,1b}$,$J_{1a,2}$)	H-1b ($J_{1b,2}$)	H-2 ($J_{2,3}$)	H-3 ($J_{3,4}$)	H-4 ($J_{4,5}$)	H-5 ($J_{5,6a}$)	H-6a ($J_{6a,6b}$)	H-6b ($J_{5,6b}$)	reference
8a (D-glucitol)[b]	+23.1	3.82 (-12.0,4.4)	3.71 (6.9)	4.10 (4.5)	4.16 (2.5)	4.00 (4.3)	3.81 (3.8)	3.76 (-12.0)	3.67 (6.0)	11c
8b (D-altritol)[c]	+44.5	3.84 (-11.7,4.8)	3.75 (7.0)	4.14 (3.6)	4.27 (4.5)	4.20 (8.0)	3.92 (2.8)	3.81 (-12.4)	3.66 (5.0)	11f
8c (D-iditol)	-6.5	3.58 (-11.8,4.6)	3.51 (6.8)	4.04[d] (3.3)	4.01[d] -	4.01 (3.3)	4.04 (4.6)	3.58 (-11.8)	3.51 (6.8)	11e,g
10a (D-mannitol)	+57.0	3.58 (-12.4,3.2)	3.49 (5.4)	3.70 (7.3)	3.86 -	3.86 (7.3)	3.70 (3.2)	3.58 (-12.4)	3.49 (5.4)	11d,e
10b (allitol)	0[e]	3.77 (-12.4,3.4)	3.63 (5.3)	3.93 (5.4)	4.04 -	4.04 (5.4)	3.93 (3.4)	3.77 (-12.4)	3.63 (5.3)	-
10c (D-gulitol)[b]	-23.1	3.76 (-12.0,3.8)	3.67 (6.0)	3.81 (4.3)	4.00 (2.5)	4.16 (4.5)	4.10 (4.4)	3.82 (-12.0)	3.71 (6.9)	11c
- (galactitol)[f]	0[e]	3.81 (-12.0,4.1)	3.72 (6.2)	4.06 (5.7)	4.40 -	4.40 (5.7)	4.06 (4.1)	3.81 (-12.0)	3.72 (6.2)	-

[a]For ^{13}C NMR data, see reference 11a,b
[b]**8a** and **10c** are enantiomers
[c]Also 2,5-anhydro-D-talitol
[d]Interchangeable
[e]*meso*-compound
[f]See Chapter 2

2,5-Anhydro-3,4,6-tri-*O*-benzyl-D-mannitol (9a) - Unmasking of the 4:1 mixture of **6a** and **4a** (0.31 g, 0.55 mmol) in the presence of KBr and AcOOH was executed as described in the general procedure to give **9a** and **7a** as a mixture of epimers after silica gel column chromatography. Yield 0.16 g (65%). R_f 0.1 (Et_2O/light petroleum, 1/1, v/v). Compound **9a**: $^{13}C\{^1H\}$ NMR: δ 138.8, 138.5 (Cq, arom), 128.5-127.7 (CH, arom), 84.4, 84.0, 82.0, 80.2 (C-2, C-3, C-4, C-5), 73.1, 72.0, 71.3, 70.0 (CH_2, Bn, C-6), 62.5 (C-1).

2,5-Anhydro-D-mannitol (10a) - Hydrogenation of the mixture of **9a** and **7a** (0.16 g, 0.37 mmol, ratio 5:1) according to the general procedure afforded pure **10a** after selective crystallization from EtOH. Yield 33 mg (55%). R_f 0.70 (MeOH). Mp 97-99°C (Lit.[11d] 101-101.5°C). ^{1}H NMR: Table 3. $^{13}C\{^1H\}$ NMR (H_2O): δ 84.7 (C-3, C-4), 78.8 (C-2, C-5), 63.6 (C-1, C-6).

3,4,6-Tri-*O*-benzyl-1-deoxy-1-dimethylphenylsilyl-D-altritol (3b-*syn*) + 3,4,6-tri-*O*-benzyl-1-deoxy-1-dimethylphenylsilyl-D-allitol (3b-*anti*) - 2,3,5-tri-*O*-benzyl-D-ribose[16] (1.39 g, 3.3 mmol) was treated with Grignard reagent **1** to give the silane **3b** as an intractable mixture of 2,3-*syn* and 2,3-*anti*-diastereomers (ratio 4:1) after purification by silica gel column chromatography. Yield

1.64 g (87%). R_f 0.6 (toluene/EtOAc, 3/2, v/v). Compound **3b**-*syn*: $^{13}C\{^1H\}$ NMR: δ 139.1, 137.8, 137.6 (Cq, arom), 133.4-127.5 (CH, arom), 82.3, 80.3 (C-3, C-4), 70.1, 68.7 (C-2, C-5), 73.4, 73.0 (CH_2, Bn), 71.1 (C-6), 21.1 (C-1), -1.9, -2.9 ($SiCH_3$). Compound **3b**-*anti*: $^{13}C\{^1H\}$ NMR: δ 138.1, 137.8, 137.5 (Cq, arom), 133.5-127.5 (CH, arom), 83.6, 79.6 (C-3, C-4), 69.8, 69.3 (C-2, C-5), 73.4, 72.8 (CH_2, Bn), 71.3 (C-6), 20.4 (C-1), -1.9, -2.6 ($SiCH_3$).

*BF_3·Et_2O-mediated cyclization of **3b*** - Cyclization of the mixture of epimers **3b** (1.14 g, 2.0 mmol) was executed as described above to give 2,5-anhydro-3,4,6-tri-*O*-benzyl-1-deoxy-1-dimethylphenylsilyl-D-altritol (**4b**) and 2,5-anhydro-3,4,6-tri-*O*-benzyl-1-deoxy-1-dimethylphenylsilyl-D-allitol (**6b**) as an intractable mixture (ratio 10:3) after chromatography (elution: Et_2O/light petroleum, 1/2, v/v). Yield 0.39 g (35%). R_f 0.9 (Et_2O/light petroleum, 3/1, v/v). Compound **4b**: $^{13}C\{^1H\}$ NMR: δ 138.6, 138.0 (Cq, arom), 133.6-127.4 (CH, arom), 80.3, 79.2, 78.7, 77.9 (C-2, C-3, C-4, C-5), 73.2, 72.8, 72.4 (CH_2, Bn), 70.3 (C-6), 16.8 (C-1), -2.0, -2.4 ($SiCH_3$). Compound **6b**: $^{13}C\{^1H\}$ NMR: δ 139.3, 138.3 (Cq, arom), 133.0-127.4 (CH, arom), 83.5, 81.1, 77.3 (C-2, C-3, C-4, C-5), 73.3, 71.9, 71.6 (CH_2, Bn), 70.7 (C-6), 21.5 (C-1), -1.6, -1.9 ($SiCH_3$). Further elution with Et_2O/light petroleum (1/1, v/v) gave 3,4,6-tri-*O*-benzyl-1,2-dideoxy-D-*ribo*-hex-1-enitol (**5b**). Yield 0.48 g (58%). R_f 0.4 (Et_2O/light petroleum, 3/1, v/v). ^1H NMR: δ 7.40-7.25 (m, 15H, H-arom), 5.92 (ddd, 1H, H-2, $J_{1a,2}$ 16.3 Hz, $J_{1b,2}$ 11.2 Hz, $J_{2,3}$ 7.9 Hz), 5.39-5.32 (m, 2H, H-1), 4.68 (AB, 2H, CH_2, Bn, J -10.9 Hz), 4.52 (AB, 2H, CH_2, Bn, J -12.0 Hz), 4.51 (s, 2H, CH_2, Bn), 4.18 (dd, 1H, H-3, $J_{3,4}$ 4.0 Hz), 3.82 (m, 1H, H-5), 3.70 (dd, 1H, H-4, $J_{4,5}$ 7.6 Hz), 3.61 (m, 2H, H-6), 2.69 (d, 1H, OH, J 4.7 Hz). $^{13}C\{^1H\}$ NMR: δ 138.4, 138.3 (Cq, arom), 135.0 (C-2), 129.2-127.3 (CH, arom), 119.5 (C-1), 81.9, 80.9 (C-3, C-4), 70.6 (C-5), 73.9, 73.2, 71.0 (CH_2, Bn), 70.3 (C-6).

2,5-Anhydro-3,4,6-tri-*O*-benzyl-D-altritol (7b) + 2,5-anhydro-3,4,6-tri-*O*-benzyl-D-allitol (9b) - Oxidative unmasking of the 10:3 mixture of silanes **4b** and **6b** (0.39 g, 0.17 mmol) was executed as described in the general procedure. The diastereomeric alcohols **7b** and **9b** were separated by silica gel column chromatography, elution was effected with Et_2O/light petroleum (1/2, v/v). The first compound isolated was **9b**. Yield 11 mg (15%). R_f 0.4 (Et_2O/light petroleum, 3/1, v/v). ^1H NMR: δ 7.34-7.22 (m, 15H, H-arom), 4.59 (s, 2H, CH_2, Bn), 4.52 (AB, 2H, CH_2, Bn, J -12.0 Hz), 4.47 (AB, 2H, CH_2, Bn, J -12.0 Hz), 4.18-4.00 (m, 4H, H-2, H-3, H-4, H-5), 3.82-3.74 (m, 1H, H-1a, $J_{1a,1b}$ -10.5 Hz), 3.70 (dd, 1H, H-1b, $J_{1b,2}$ 2.8 Hz), 3.60 (m, 2H, H-6, $J_{5,6}$ 2.6 Hz, $J_{6a,6b}$ -10.2 Hz), 2.70 (bd, 1H, OH). $^{13}C\{^1H\}$ NMR: δ 138.0, 137.6 (Cq, arom), 128.4-127.7 (CH, arom), 82.9, 80.8, 77.8 (C-2, C-3, C-4, C-5), 73.4, 72.8, 72.7 (CH_2, Bn), 69.5 (C-6), 63.1 (C-1). Elution with Et_2O/light petroleum (1/1, v/v) gave **7b**. Yield 38 mg (52%). R_f 0.3 (Et_2O/light petroleum, 3/1, v/v). ^1H NMR: δ 7.33-7.25 (m, 15H, H-arom), 4.60 (AB, 2H, CH_2, Bn, J -11.5 Hz), 4.59 (s, 2H, CH_2, Bn), 4.54 (s, 2H, CH_2, Bn), 4.31-3.98 (m, 4H, H-2, H-3, H-4, H-5), 3.86-3.79 (m, 2H, H-1), 3.58 (d, 1H, H-6a, $J_{5,6a}$ 3.6 Hz, $J_{6a,6b}$ -10.6 Hz), 3.48 (dd, 1H, H-6b, $J_{5,6b}$ 3.7 Hz), 2.55 (m, 1H, OH). $^{13}C\{^1H\}$ NMR: δ 138.1, 137.9 (Cq, arom), 128.4-127.6 (CH, arom), 80.7, 79.6, 78.6, 78.1 (C-2, C-3, C-4, C-5), 73.5, 73.1, 72.6 (CH_2, Bn), 70.2 (C-6), 62.2 (C-1).

2,5-Anhydro-D-altritol (8b) - Compound **7b** (38 mg, 0.088 mmol) was hydrogenated as described above, to give crude **8b** as an oil. Yield 14 mg (99%). R_f 0.4 (MeOH). ^1H NMR: Table 3. $^{13}C\{^1H\}$ NMR (CD_3OD): δ 83.4, 82.3 (C-3, C-4), 73.5, 73.3 (C-2, C-5), 63.2 (C-6), 62.2 (C-1).

2,5-Anhydro-allitol (10b) - As decribed in the general procedure, hydrogenation of compound **9b** (20 mg, 0.046 mmol) afforded crude **10b**. Yield 6.9 mg (92%). R_f 0.2 (MeOH). ^1H NMR: Table 3. $^{13}C\{^1H\}$ NMR (CD_3OD): δ 85.3 (C-3, C-4), 72.7 (C-2, C-5), 63.2 (C-6).

H_2SO_4-mediated cyclization of 3b - Cyclization of **3b** (0.50 g, 0.88 mmol) in the presence of H_2SO_4 was performed as described above, to give **4b** and **6b** as an intractable mixture (ratio 2:9) after purification. Yield 0.36 g (74%). Olefin **5b** was isolated as a minor product. Yield 66 mg (18%).

3,4,6-Tri-*O*-benzyl-1-deoxy-1-dimethylphenylsilyl-D-iditol (3c-*syn*) + 3,4,6-tri-*O*-benzyl-1-deoxy-1-dimethylphenylsilyl-D-gulitol (3c-*anti*) - 2,3,5-tri-*O*-benzyl-D-xylose[17] (0.73 g, 1.74 mmol) was treated with Grignard reagent **1** to give silane **3c** as an intractable mixture of 2,3-*syn* and 2,3-*anti*-diastereomers (ratio 5:2) after purification by silica gel column chromatography. Yield 0.65 g (66%). R_f 0.7 (toluene/EtOAc, 3/2, v/v). Compound **3c-*syn***: $^{13}C\{^1H\}$ NMR: δ 138.7, 137.9 (Cq, arom), 133.4-126.6 (CH, arom), 81.6, 76.6 (C-3, C-4), 67.9, 67.3 (C-2, C-5), 74.1, 73.9, 73.0 (CH_2, Bn), 70.9 (C-6), 22.3 (C-1), -2.0, -2.8 ($SiCH_3$). Compound **3c-*anti***: $^{13}C\{^1H\}$ NMR: δ 138.8, 137.9 (Cq, arom), 133.4-126.6 (CH, arom), 82.2, 78.1 (C-3, C-4), 69.4, 69.2 (C-2, C-5), 74.1, 73.9, 73.2 (CH_2, Bn), 71.1 (C-6), 20.2 (C-1), -1.9, -2.5 ($SiCH_3$).

$BF_3{\cdot}Et_2O$-mediated cyclization of 3c - Cyclization of the mixture of diastereomers **3c** (0.35 g, 0.61 mmol) with $BF_3{\cdot}Et_2O$ was performed as described above to afford 2,5-anhydro-3,4,6-tri-*O*-benzyl-1-deoxy-1-dimethylphenylsilyl-D-iditol (**4c**) as an oil after purification on silica gel (elution: Et_2O/light petroleum, 1/2, v/v). Yield 0.17 g (50%). R_f 0.9 (Et_2O/light petroleum, 3/1, v/v). ^1H NMR: δ 7.53-7.19 (m, 20H, H-arom), 4.54 (AB, 2H, CH_2, Bn, *J* -12.0 Hz), 4.44 (s, 2H, CH_2, Bn), 4.23 (AB, 2H, CH_2, Bn, *J* -12.0 Hz), 4.25-3.96 (m, 4H, H-2, H-3, H-4, H-5), 3.70 (dd, 1H, H-6a, $J_{5,6a}$ 6.2 Hz, $J_{6a,6b}$ -9.8 Hz), 3.61 (dd, 1H, H-6b, $J_{5,6b}$ 6.4 Hz), 1.31-1.24 (m, 2H, H-1), 0.30, 0.29 (2x s, 6H, $SiCH_3$). $^{13}C\{^1H\}$ NMR: δ 138.8, 138.4, 138.1 (Cq, arom), 133.6-127.3 (CH, arom), 82.7, 81.6, 78.0, 77.8 (C-2, C-3, C-4, C-5), 73.3, 72.3, 71.3 (CH_2, Bn), 68.7 (C-6), 15.9 (C-1), -2.0, -2.6 ($SiCH_3$). Further elution with Et_2O/light petroleum (1/1, v/v) gave 3,4,6-tri-*O*-benzyl-1,2-dideoxy-D-*xylo*-hex-1-enitol (**5c**). Yield 97 mg (38%). R_f 0.4 (Et_2O/light petroleum, 3/1, v/v). ^1H NMR: δ 7.35-7.26 (m, 15H, H-arom), 5.86 (ddd, 1H, H-2, $J_{1a,2}$ 10.7 Hz, $J_{1b,2}$ 16.3 Hz, $J_{2,3}$ 8.6 Hz), 5.40-5.32 (m, 2H, H-1), 4.71 (AB, 2H, CH_2, Bn, *J* -10.7 Hz), 4.49 (AB, 2H, CH_2, Bn, *J* -11.5 Hz), 4.44 (s, 2H, CH_2, Bn), 4.10 (m, 1H, H-3), 3.80 (m, 1H, H-5), 3.61 (dd, 1H, H-4), 3.42 (d, 2H, H-6), 2.45 (d, 1H, OH, *J* 6.9 Hz). $^{13}C\{^1H\}$ NMR: δ 138.1, 138.0 (Cq, arom), 135.1 (C-2), 128.2-127.5 (CH, arom), 119.3 (C-1), 82.1, 80.2 (C-3, C-4), 75.0, 73.2, 71.1 (CH_2, Bn), 70.6 (C-6), 69.9 (C-5).

2,5-Anhydro-3,4,6-tri-*O*-benzyl-D-iditol (7c) - Oxidative unmasking of **4c** (0.17 g, 0.31 mmol) was executed as described in the general procedure. The oily residue obtained after work-up was purified by silica gel column chromatography, elution was effected with Et_2O/light petroleum (1/2, v/v), to give pure **7c** as an oil. Yield 98 mg (73%). R_f 0.3 (Et_2O/light petroleum, 3/1, v/v). ^1H NMR: δ 7.35-7.26 (m, 15H, H-arom), 4.59-4.43 (m, 6H, CH_2, Bn), 4.33, 4.25 (2x m, 2H, H-2, H-5), 4.10 (m, 2H, H-3, H-4), 3.83-3.70 (m, 4H, H-1, H-6), 2.15 (bs, 1H, OH). $^{13}C\{^1H\}$ NMR: δ 138.0, 137.7, 137.3 (Cq, arom), 128.5-127.5 (CH, arom), 82.5, 81.5, 79.7, 78.8 (C-2, C-3, C-4, C-5), 73.4, 72.2, 72.1 (CH_2, Bn), 68.3, 61.7 (C-1, C-6).

2,5-Anhydro-D-iditol (8c) - Compound **7c** (98 mg, 0.23 mmol) was hydrogenated as described above, to give crude **8c** as an oil. Yield 37 mg (100%). R_f 0.1 (MeOH). Crystallization from EtOH afforded white crystals (20 mg). Mp 113-115°C (Lit.[11e,g] 119°C). ^1H NMR: Table 3. $^{13}C\{^1H\}$ NMR (CD_3OD): δ 81.9 (C-2, C-5), 78.5 (C-3, C-4), 61.8 (C-1, C-6).

H_2SO_4-mediated cyclization of 3c - Cyclization of **3c** (0.30 g, 0.53 mmol) in the presence of H_2SO_4 was performed as described above, to give **4c** and 2,5-anhydro-3,4,6-tri-*O*-benzyl-1-deoxy-

1-dimethylphenylsilyl-D-gulitol (**6c**) as an intractable mixture (ratio 1:2) after purification. Yield 78 mg (27%). Compound **6c**: $^{13}C\{^1H\}$ NMR: δ 138.6, 138.3, 138.1 (Cq, arom), 133.7-127.3 (CH, arom), 83.7, 81.2, 78.4, 78.1 (C-2, C-3, C-4, C-5), 73.1, 72.0, 71.5 (CH_2, Bn), 68.9 (C-6), 18.9 (C-1), -2.0, -2.6 ($SiCH_3$). Olefin **5c** was isolated as the major product. Yield 0.13 g (60%).

2,5-Anhydro-3,4,6-tri-*O*-benzyl-D-iditol (7c) + 2,5-anhydro-3,4,6-tri-*O*-benzyl-D-gulitol (9c) - Oxidative unmasking of the 1:2 diastereomeric mixture of **4c** and **6c** (78 mg, 0.14 mmol) was executed as described in the general procedure. The oily residue obtained after work-up was purified by silica gel column chromatography, elution was effected with Et_2O/light petroleum (1/2, v/v) to give pure **7c** as an oil. Yield 16 mg (25%). Further elution with Et_2O/light petroleum (1/3, v/v) afforded pure **9c**. Yield 31 mg (51%). R_f 0.2 (Et_2O/light petroleum, 3/1, v/v). ^1H NMR: δ 7.35-7.25 (m, 15H, H-arom), 4.57 (AB, 2H, CH_2, Bn, J -12.0 Hz), 4.53 (AB, 2H, CH_2, Bn, J -11.8 Hz), 4.48 (AB, 2H, CH_2, Bn, J -12.0 Hz), 4.35, 4.33 (2x dd, H-2, H-5), 4.05, 3.98 (2x d, 2H, H-3, H-4), 3.75-3.68 (m, 4H, H-1, H-6), 2.27 (bs, 1H, OH). $^{13}C\{^1H\}$ NMR: δ 138.0, 137.7, 137.3 (Cq, arom), 128.5-127.5 (CH, arom), 84.5, 82.8, 82.3, 80.0 (C-2, C-3, C-4, C-5), 73.5, 71.9, 71.6 (CH_2, Bn), 68.2 (C-6), 63.0 (C-1).

2,5-Anhydro-D-gulitol (10c) - As decribed in the general procedure, hydrogenation of compound **9c** (20 mg, 0.046 mmol) afforded crude **10c**, the enantiomer of **8a**. Yield 6.9 mg (92%).

Preparation of dithioacetals 11a-c[21] - To a well-stirred suspension of the diethyl dithioacetals of D-arabinose[39a], D-ribose[39b] or D-xylose[39c] (20 mmol) in acetone (100 mL), 2,2-dimethoxypropane (5 mL, 40 mmol) and pyridinium *p*-toluenesulfonate (0.5 g, 2.0 mmol) were added and the reaction was monitored by TLC (EtOAc/light petroleum, 1/1, v/v). After 1-1.5 h the reaction was complete and the mixture became homogeneous. The mixture was quenched with saturated $NaHCO_3$ solution (30 mL), concentrated and the residue taken up in EtOAc (80 mL). The organic layer was washed with $NaHCO_3$ solution (2x 20 mL), dried ($MgSO_4$), concentrated *in vacuo* and coevaporated with toluene to give the crude product which was crystallized from light petroleum. The crystals were dried *in vacuo*, dissolved in THF (100 mL) and benzyl bromide was added (2.3 equiv). The solution was cooled to 0°C and NaH (2.2 equiv, 60% in oil) was added in portions. The mixture was stirred until TLC-analysis (Et_2O/light petroleum, 1/1, v/v) indicated the presence of a single highly lipophilic product. Et_2O (150 mL) and saturated NH_4Cl (20 mL) were added and the layers were separated. The organic layer was washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The oily residue was purified by column chromatography, elution was effected with Et_2O/light petroleum (1/4→1/3, v/v) to give **11a**, **11b** or **11c**.

2,3-Di-*O*-benzyl-4,5-*O*-isopropylidene-D-arabinose diethyl dithioacetal (11a) - ^1H NMR: δ 7.40-7.25 (m, 10H, H-arom), 4.83 (AB, 2H, CH_2, Bn, J -10.9 Hz), 4.77 (s, 2H, CH_2, Bn), 4.22 (m, 1H, H-4), 4.18-4.11 (m, 1H, H-3), 4.14 (d, 1H, H-1, $J_{1,2}$ 6.4 Hz), 4.02 (dd, 1H, H-5a, $J_{4,5a}$ 6.1 Hz, $J_{5a,5b}$ -8.2 Hz), 3.87 (dd, 1H, H-5b, $J_{4,5b}$ 6.5 Hz), 3.79 (dd, 1H, H-2, $J_{2,3}$ 4.3 Hz), 2.75-2.60 (m, 4H, CH_2, SEt), 1.41, 1.33 (2x s, 6H, CH_3, isoprop), 1.28-1.19 (m, 6H, CH_3, SEt). $^{13}C\{^1H\}$ NMR: δ 138.4, 138.3 (Cq, arom), 128.2-127.5 (CH, arom), 108.7 (Cq, isoprop), 83.2, 80.0, 76.6 (C-2, C-3, C-4), 75.2, 74.8 (CH_2, Bn), 66.8 (C-6), 53.0 (C-1), 26.6, 25.2 (CH_3, isoprop), 25.8, 24.8 (CH_2, SEt), 14.4 (CH_3, Et).

2,3-Di-*O*-benzyl-4,5-*O*-isopropylidene-D-ribose diethyl dithioacetal (11b) - ^1H NMR: δ 7.52-7.15 (m, 10H, H-arom), 4.92-4.63 (m, 4H, CH_2, Bn), 4.44 (d, 1H, H-1, $J_{1,2}$ 5.7 Hz), 4.41 (dt, 1H, H-4, $J_{3,4}$ 3.8 Hz, $J_{4,5a}$ $J_{4,5b}$ 6.9 Hz), 4.11 (dd, 1H, H-3, $J_{2,3}$ 4.8 Hz), 3.96 (dd, 1H, H-5a, $J_{5a,5b}$ -8.0

Hz), 3.80 (dd, 1H, H-5b), 3.67 (dd, 1H, H-2), 2.90-2.66 (m, 4H, CH_2, SEt), 1.45, 1.31 (2x s, 6H, CH_3, isoprop), 1.26-1.12 (2x s, 6H, $SiCH_3$). $^{13}C\{^1H\}$ NMR: δ 138.3, 137.6 (Cq, arom), 128.1-127.4 (CH, arom), 108.2 (Cq, isoprop), 82.5, 78.8, 75.9 (C-2, C-3, C-4), 75.7, 73.9 (CH_2, Bn), 64.9 (C-6), 53.0 (C-1), 26.2, 25.0 (CH_3, isoprop), 25.4, 25.1 (CH_2, SEt), 14.2 (CH_3, Et).

2,3-Di-*O*-benzyl-4,5-*O*-isopropylidene-D-xylose diethyl dithioacetal (11c) - ^1H NMR: δ 7.36-7.24 (m, 10H, H-arom), 4.82 (AB, 2H, CH_2, Bn, *J* -11.3 Hz), 4.74 (s, 2H, CH_2, Bn), 4.37 (ddd, 1H, H-4, $J_{3,4}$ 5.6 Hz, $J_{4,5a}$ 6.4 Hz, $J_{4,5b}$ 7.5 Hz), 4.14 (d, 1H, H-1, $J_{1,2}$ 3.9 Hz), 3.96-3.88 (m, 2H, H-2, H-5a), 3.82 (t, 1H, H-3, $J_{2,3}$ 5.6 Hz), 3.77 (dd, 1H, H-5b, $J_{5a,5b}$ -8.1 Hz), 2.74 (dq, 2H, CH_2, SEt, *J* -3.0, 7.3 Hz), 2.62 (q, 2H, CH_2, SEt, *J* 7.3 Hz), 1.43, 1.34 (2x s, 6H, CH_3, isoprop), 1.25 (t, 3H, CH_3, SEt), 1.24 (t, 3H, CH_3, SEt). $^{13}C\{^1H\}$ NMR: δ 138.3, 138.1 (Cq, arom), 128.0-127.3 (CH, arom), 108.7 (Cq, isoprop), 82.6, 79.7, 76.3 (C-2, C-3, C-4), 74.4 (CH_2, Bn), 65.6 (C-6), 52.4 (C-1), 26.3, 25.5 (CH_3, isoprop), 25.4, 25.0 (CH_2, SEt), 14.2 (CH_3, Et).

General procedure for hydrolysis of thioacetals 11a,b and 18c with HgO and $BF_3{\cdot}Et_2O$[22] - Red mercury(II) oxide (0.87 g, 4.0 mmol), $BF_3{\cdot}Et_2O$ (0.49 mL, 4.0 mmol) and 85% aqueous THF (5 mL) were stirred vigorously, while a solution of a dithioacetal (2 mmol) in THF (1 mL) was added dropwise under N_2. The mixture was stirred until TLC-analysis (Et_2O/light petroleum, 1/1, v/v) indicated the conversion was complete (1-1.5 h). Et_2O (20 mL) was added and the reaction mixture was neutralized with anhydrous Na_2CO_3 (1.5 g). The salts were removed by filtration and the filtrate was concentrated to give the corresponding aldehyde, which was used immediately in the next step.

General procedure for the nucleophilic addition of 1 to the open-chain aldehydes - The aldehyde obtained by hydrolysis of the thioacetals **11a,b** or **18c** (1 mmol) was coevaporated with toluene (2x 2 mL) and dissolved in dry THF or Et_2O (5 mmol). The solution was cooled (0°C), a 1 M solution of **1** in the same solvent was added slowly, and stirring continued until TLC-analysis (Et_2O/light petroleum, 1/1, v/v) indicated the reaction to be complete (1-2 h). Work-up was performed as described above for the addition of **1** to **2a-c**.

3,4-Di-*O*-benzyl-1-deoxy-1-dimethylphenylsilyl-5,6-*O*-isopropylidene-D-glucitol (12a) - The aldehyde obtained from hydrolysis of **11a** (7.10 g, 14.92 mmol) in Et_2O was treated with **1** according to the general procedure for open-chain aldehydes. The oil obtained after extraction was applied onto a column of silica gel and elution was effected with Et_2O/light petroleum (1/4→1/3, v/v) to afford **12a** as an oil. Yield 7.0 g (90%). R_f 0.8 (Et_2O/light petroleum, 1/1, v/v). $[\alpha]_D^{20}$ +9.7 (c 1). ^1H NMR: δ 7.53-7.24 (m, 15H, H-arom), 4.63 (d, 2H, CH_2, Bn, *J* -1.3 Hz), 4.62 (AB, 2H, CH_2, Bn, *J* -11.1), 4.23 (q, 1H, H-5, $J_{4,5}$ $J_{5,6a}$ $J_{5,6b}$ 6.4 Hz), 4.00 (dd, 1H, H-6a, $J_{6a,6b}$ -8.4 Hz), 3.89 (dd, 1H, H-6b, $J_{5,6b}$ 6.8 Hz), 3.87 (m, 1H, H-2), 3.78 (t, 1H, H-4, $J_{3,4}$ $J_{4,5}$ 5.2 Hz), 3.33 (t, 1H, H-3, $J_{2,3}$ 4.5 Hz), 2.35 (d, 1H, OH, *J* 6.8 Hz), 1.40, 1.31 (2x s, 6H, CH_3, isoprop), 1.11 (dd, 1H, H-1a, $J_{1a,1b}$ -14.1 Hz, $J_{1a,2}$ 9.6 Hz), 0.98 (dd, 1H, H-1b, $J_{1b,2}$ 4.7 Hz), 0.33, 0.32 (2x s, 6H, $SiCH_3$). $^{13}C\{^1H\}$ NMR: δ 139.0, 137.9 (Cq, arom), 133.3, 128.5-127.4 (CH, arom), 108.3 (Cq, isoprop), 84.5, 78.9, 76.2 (C-3, C-4, C-5), 74.5, 74.1 (CH_2, Bn), 68.2 (C-2), 66.2 (C-6), 26.3, 24.8 (CH_3, isoprop), 21.5 (C-1), -2.0, -2.7 ($SiCH_3$).

General procedure for deacetonation - An isopropylidene compound (1 mmol) was dissolved in 80% aqueous AcOH/H_2O (5 mL) and stirring continued until TLC-analysis (Et_2O/light petroleum, 3/1, v/v) showed the reaction to be complete (10-16 h). Solvents were evaporated, the residue coevaporated with toluene (4x 2 mL) and purified by silica gel column chromatography.

3,4-Di-*O*-benzyl-1-deoxy-1-dimethylphenylsilyl-D-glucitol (13a) - Compound **12a** (1.57 g, 3.08 mmol) was deacetonated as described in the general procedure to give triol **12a** as an oil. Yield 1.25 g (86%). R_f 0.3 (Et_2O/light petroleum, 3/1, v/v). $[\alpha]_D^{20}$ +6.9 (c 2). ^1H NMR: δ 7.52-7.22 (m, 15H, H-arom), 4.55 (AB, 2H, CH_2, Bn, J -11.1 Hz), 4.53 (s, 2H, CH_2, Bn), 4.08 (m, 1H, H-5), 3.84 (m, 1H, H-2), 3.74-3.62 (m, 3H, H-4, H-6), 3.38 (dd, 1H, H-3, $J_{2,3}$ 3.2 Hz, $J_{3,4}$ 4.3 Hz), 2.30 (bs, 1H, OH), 2.20 (bs, 1H, OH), 1.62 (s, 1H, OH), 1.17 (dd, 1H, H-1a, $J_{1a,1b}$ -14.7 Hz, $J_{1a,2}$ 9.2 Hz), 1.05 (dd, 1H, H-1b, $J_{1b,2}$ 5.2 Hz), 0.33, 0.32 (2x s, 6H, $SiCH_3$). $^{13}C\{^1H\}$ NMR: δ 138.9, 137.7, 137.6 (Cq, arom), 133.3, 128.6-127.5 (CH, arom) 83.4, 77.6 (C-3, C-4), 73.2 (C-5), 73.9, 73.2 (CH_2, Bn), 67.9 (C-2), 63.2 (C-6), 21.7 (C-1), -2.0, -2.9 ($SiCH_3$).

BF_3·Et_2O-mediated cyclization of 13a - Cyclization of triol **13a** (0.38 g, 0.79 mmol) with BF_3·Et_2O was executed as described in the general procedure to give two products (R_f 0.3 and R_f 0.7) as indicated by TLC analysis (toluene/acetone, 85/15, v/v). The oil obtained after work-up was applied onto a column of silica gel, which was eluted with Et_2O/light petroleum (1/1→2/1, v/v) to give 2,5-anhydro-3,4-di-*O*-benzyl-1-deoxy-1-dimethylphenylsilyl-D-glucitol (**14a**). Yield 0.19 g (53%). R_f 0.7 (toluene/acetone, 85/15, v/v). $[\alpha]_D^{20}$ +36.2 (c 2). MS (m/z): 463 $[M+H]^+$, 485 $[M+Na]^+$. ^1H NMR: δ 7.55-7.25 (m, 15H, H-arom), 4.47 (s, 2H, CH_2, Bn), 4.30 (AB, 2H, CH_2, Bn, J -12.1 Hz), 4.12 (m, 1H, H-2), 3.92 (m, 2H, H-5, H-6a), 3.74 (dd, 1H, H-6b, $J_{5,6b}$ 1.8 Hz, $J_{6a,6b}$ -9.8 Hz), 3.63 (d, 1H, H-4, $J_{4,5}$ 3.7 Hz), 3.56 (d, 1H, H-3, $J_{2,3}$ 3.2 Hz), 1.38 (dd, 1H, H-1a, $J_{1a,1b}$ -14.2 Hz, $J_{1a,2}$ 7.3 Hz), 1.20 (dd, 1H, H-1b, $J_{1b,2}$ 7.5 Hz), 0.31 (s, 6H, $SiCH_3$). $^{13}C\{^1H\}$ NMR: δ 138.8, 137.6 (Cq, arom), 133.4, 128.6-127.9 (CH, arom), 83.6, 83.2, 79.0 (C-2, C-3, C-4, C-5), 71.7, 70.8 (CH_2, Bn), 63.0 (C-6), 15.2 (C-1), -2.3, -2.7 ($SiCH_3$). Further elution with Et_2O/light petroleum (2/1, v/v) gave **14a'**. Yield 5.8 mg (1.6%). R_f 0.7 (Et_2O/light petroleum, 3/1, v/v). ^1H NMR: δ 7.54-7.20 (m, 15H, H-arom), 4.43 (AB, 2H, CH_2, Bn, J -11.8 Hz), 4.31 (AB, 2H, CH_2, Bn, J -11.6 Hz), 4.22 (ddd, 1H, H-2, $J_{1a,2}$ 7.6 Hz, $J_{1b,2}$ 7.3 Hz, $J_{2,3}$ 3.5 Hz), 4.13 (q, 1H, H-5), 4.04 (dd, 1H, H-4, $J_{3,4}$ 1.5 Hz, $J_{4,5}$ 5.3 Hz), 3.77 (dd, 1H, H-6a, $J_{5,6a}$ 5.5 Hz, $J_{6a,6b}$ -11.6 Hz), 3.67 (dd, 1H, H-6b, $J_{5,6b}$ 4.9 Hz), 3.60 (dd, 1H, H-3), 1.32 (dd, 1H, H-1a, $J_{1a,1b}$ -14.3 Hz), 1.19 (dd, 1H, H-1b), 0.33, 0.31 (2x s, 6H, $SiCH_3$). $^{13}C\{^1H\}$ NMR: δ 138.9, 137.8, 137.4 (Cq, arom), 133.5, 128.7-127.3 (CH, arom), 82.9, 82.7 (C-3, C-4), 78.5, 77.5 (C-2, C-5), 72.2, 71.5 (CH_2, Bn), 61.6 (C-6), 15.7 (C-1), -2.2, -2.7 ($SiCH_3$). Further elution with Et_2O/light petroleum (3/1, v/v) gave 3,4-di-*O*-benzyl-1,2-dideoxy-D-*arabino*-hex-1-enitol (**15a**). Yield 73 mg (28%). R_f 0.3 (toluene/acetone, 85/15, v/v). $[\alpha]_D^{20}$ -0.4 (c 2). ^1H NMR: δ 7.38-7.25 (m, 10H, H-arom), 5.96 (ddd, 1H, H-2, $J_{1a,2}$ 10.9 Hz, $J_{1b,2}$ 16.7 Hz, $J_{2,3}$ 8.3 Hz), 5.44-5.33 (m, 2H, H-1), 4.63 (AB, 2H, CH_2, Bn, J -11.3 Hz), 4.53 (AB, 2H, CH_2, Bn, J -12.0 Hz), 4.10 (ddd, 1H, H-5, $J_{4,5}$ 1.0 Hz, $J_{5,6a}$ 3.5 Hz, $J_{5,6b}$ 7.2 Hz), 3.80 (m, 1H, H-3), 3.69-3.64 (m, 3H, H-4, H-6. $^{13}C\{^1H\}$ NMR: δ 137.8, 137.5 (Cq, arom), 134.2 (C-2), 128.4-127.8 (CH, arom), 119.3 (C-1), 80.3, 80.0 (C-3, C-4), 74.0, 70.7 (CH_2, Bn), 71.1 (C-5), 63.2 (C-6).

Oxidative unmasking of compound 14a - Compound **14a** (0.39 g, 0.84 mmol) was oxidatively unmasked as described in the general procedure to give 2,5-anhydro-3,4-di-*O*-benzyl-D-glucitol as an oil. Yield 0.23 g (81%). R_f 0.3 (Et_2O). $[\alpha]_D^{20}$ -32.8 (c 1). ^1H NMR: δ 7.52-7.25 (m, 10H, H-arom), 4.56 (s, 2H, CH_2, Bn), 4.53 (AB, 2H, CH_2, Bn, J -11.8 Hz), 4.18-3.83 (m, 6H, H-1a, H-2, H-4, H-5, H-6), 3.80 (d, 1H, H-3, $J_{2,3}$ 2.8 Hz), 3.66 (dd, 1H, H-1b, $J_{1a,1b}$ -12.0 Hz, $J_{1b,2}$ 4.3 Hz). $^{13}C\{^1H\}$ NMR: δ 137.4, 137.0 (Cq, arom), 128.2-127.3 (CH, arom), 83.5, 83.2, 82.6, 80.4 (C-2, C-3, C-4, C-5), 71.7, 71.5 (CH_2, Bn), 62,4, 61.5 (C-1, C-6).
Hydrogenation of 2,5-anhydro-3,4-di-*O*-benzyl-D-glucitol gave **8a**. Yield 0.10 g (95%).

H_2SO_4-mediated cyclization of 13a - Cyclization of **13a** (0.23 g, 0.48 mmol) in the presence of

H_2SO_4 was performed as described above to afford, after work-up and silica gel chromatography 2,5-anhydro-3,4-di-*O*-benzyl-1-deoxy-1-dimethylphenylsilyl-D-mannitol (**16a**) and **14a** as a 4:1 mixture. Yield 95 mg (43%). R_f 0.3 (toluene/acetone, 85/15, v/v). Compound **16a**: $^{13}C\{^1H\}$ NMR: δ 138.8, 137.3 (Cq, arom), 133.5, 128.3-127.4 (CH, arom), 89.0, 85.6 (C-2, C-3), 80.7, 80.0 (C-4, C-5), 72.7, 71.5 (CH_2, Bn), 63.1 (C-6), 20.8 (C-1), -1.5, -2.0 ($SiCH_3$). Further elution gave olefin **15a**. Yield 75 mg (48%).

*Oxidative unmasking of compounds **14a** and **16a*** - Treatment of the 4:1 mixture of **16a** and **14a** (95 mg, 0.20 mmol) with KBr and AcOOH was executed as described in the general procedure to give 2,5-anhydro-3,4-di-*O*-benzyl-D-mannitol and 2,5-anhydro-3,4-di-*O*-benzyl-D-glucitol as a mixture after silica gel column chromatography. Yield 49 mg (69%). R_f 0.3 (Et_2O). $^{13}C\{^1H\}$ NMR, *manno*-isomer: δ 137.8 (Cq, arom), 128.3, 128.0, 127.3 (CH, arom), 84.2 (C-2, C-3), 81.0 (C-4, C-5), 71.7 (CH_2, Bn), 62.3 (C-1, C-6).
Hydrogenation of 2,5-anhydro-3,4-di-*O*-benzyl-D-mannitol gave **10a**. Yield 18 mg (77%).

3,4-Di-*O*-benzyl-1-deoxy-1-dimethylphenylsilyl-5,6-*O*-isopropylidene-D-altritol (12b) - The aldehyde obtained from hydrolysis of **11b** (5.50 g, 11.55 mmol) in Et_2O was treated with **1** according to the general procedure for open-chain aldehydes. The oil obtained after extraction was applied onto a column of silica gel and elution was effected with Et_2O/light petroleum (1/4→1/3, v/v) to afford **12b** as an oil. Yield 4.02 g (67%). R_f 0.7 (Et_2O/light petroleum, 1/1, v/v). ^1H NMR: δ 7.54-7.23 (m, 15H, H-arom), 4.68 (s, CH_2, Bn), 4.60 (AB, 2H, CH_2, Bn, *J* -11.4 Hz), 4.25 (m, 1H, H-5), 4.00-3.90 (m, 3H, H-2, H-6), 3.80 (dd, 1H, H-4, $J_{3,4}$ 3.4 Hz, $J_{4,5}$ 5.2 Hz), 3.39 (dd, 1H, H-3, $J_{2,3}$ 4.9 Hz), 2.82 (d, 1H, OH, *J* 4.1 Hz), 1.39, 1.31 (2x s, 6H, CH_3, isoprop), 1.02 (m, 1H, H-1a), 0.85 (dd, 1H, H-1b, $J_{1a,1b}$ -11.1 Hz, $J_{1b,2}$ 5.4 Hz), 0.33, 0.32 (2x s, 6H, $SiCH_3$). $^{13}C\{^1H\}$ NMR: δ 139.0, 137.7, 137.6 (Cq, arom), 133.4, 128.3-127.5 (CH, arom), 108.3 (Cq, isoprop), 83.5, 79.6 (C-3, C-4), 75.2 (C-5), 73.9, 73.6 (CH_2, Bn), 68.4 (C-2), 65.8 (C-6), 26.2, 24.9 (CH_3, isoprop), 20.7 (C-1), -1.9, -2.8 ($SiCH_3$).

3,4-Di-*O*-benzyl-1-deoxy-1-dimethylphenylsilyl-D-altritol (13b) - Compound **12b** (1.43 g, 2.75 mmol) was deacetonated as described in the general procedure to give triol **12b** as an oil. Yield 1.21 g (92%). R_f 0.4 (Et_2O/light petroleum, 3/1, v/v). $[\alpha]_D^{20}$ +9.1 (c 2). ^1H NMR: δ 7.54-7.24 (m, 15H, H-arom), 4.63 (AB, CH_2, Bn, *J* -11.1 Hz), 4.54 (s, 2H, CH_2, Bn), 3.92-3.63 (m, 4H, H-2, H-5, H-6), 3.58-3.53 (m, 2H, H-3, H-4), 1.17-1.07 (m, 2H, H-1), 0.34, 0.32 (2x s, 6H, $SiCH_3$). $^{13}C\{^1H\}$ NMR: δ 138.8, 137.6, 137.4 (Cq, arom), 133.3, 128.4-127.5 (CH, arom), 82.2, 81.1 (C-3, C-4), 73.6, 73.2 (CH_2, Bn), 70.6, 69.0 (C-2, C-5), 63.3 (C-6), 21.4 (C-1), -2.0, -3.0 ($SiCH_3$).

*BF_3·Et_2O-mediated cyclization of **13b*** - Cyclization of triol **13b** (0.34 g, 0.70 mmol) was executed as described in the general procedure to give two products (R_f 0.5 and R_f 0.8) as indicated by TLC analysis (Et_2O). The oil obtained after work-up was applied onto a column of silica gel, which was eluted with Et_2O/light petroleum (1/1→2/1, v/v) to 2,5-anhydro-3,4-di-*O*-benzyl-1-deoxy-1-dimethylphenylsilyl-D-altritol (**14b**). Yield 71 mg (22%). R_f 0.8 (Et_2O). $[\alpha]_D^{20}$ +38.3 (c 1). ^1H NMR: δ 7.54-7.26 (m, 15H, H-arom), 4.63 (AB, 2H, CH_2, Bn, *J* -11.8 Hz), 4.55 (AB, 2H, CH_2, Bn, *J* -11.8 Hz), 4.10-3.96 (m, 3H, H-2, H-5, H-6a), 3.76-3.72 (m, 2H, H-4, H-6b), 3.47 (m, 1H, H-3), 1.44 (dd, 1H, H-1a, $J_{1a,1b}$ -14.5 Hz, $J_{1a,2}$ 9.2 Hz), 1.14 (dd, 1H, H-1b, $J_{1b,2}$ 5.8 Hz), 0.33, 0.30 (2x s, 6H, CH_3Si). $^{13}C\{^1H\}$ NMR: δ 139.1, 138.5, 137.8 (Cq, arom), 133.6, 128.4-127.5 (CH, arom), 79.8, 79.7, 78.8, 78.4 (C-2, C-3, C-4, C-5), 72.9, 72.7 (CH_2, Bn), 62.5 (C-6), 16.9 (C-1), -2.0, -2.3 ($SiCH_3$). Further elution with Et_2O/light petroleum (3/1, v/v) afforded 3,4-di-*O*-benzyl-1,2-dideoxy-D-*ribo*-hex-1-enitol (**15b**). Yield 0.12 g (52%). R_f 0.5 (Et_2O). $[\alpha]_D^{20}$ +63.3 (c 2). ^1H

NMR: δ 7.40-7.25 (m, 10H, H-arom), 5.91 (ddd, 1H, H-2, $J_{1a,2}$ 16.7 Hz, $J_{1b,2}$ 11.0 Hz, $J_{2,3}$ 7.7 Hz), 5.46-5.36 (m, 2H, H-1), 4.62 (AB, 2H, CH_2, Bn, J -11.0 Hz), 4.52 (AB, 2H, CH_2, Bn, J -11.8 Hz), 4.08 (dd, 1H, H-3, $J_{3,4}$ 6.0 Hz), 3.78-3.71 (m, 3H, H-5, H-6), 3.61 (t, 1H, H-4, $J_{4,5}$ 6.2 Hz), 3.10 (d, 1H, OH, J 3.2 Hz). $^{13}C\{^1H\}$ NMR: δ 137.9, 137.7 (Cq, arom), 135.1 (C-2), 128.3-127.6 (CH, arom), 119.8 (C-1), 81.8, 81.1 (C-3, C-4), 73.9, 70.3 (CH_2, Bn), 72.0 (C-5), 63.3 (C-6).

*Oxidative unmasking of **14b*** - Treatment of **14b** (0.14 g, 0.30 mmol) with KBr and AcOOH was executed as described in the general procedure to give 2,5-anhydro-3,4-di-*O*-benzyl-D-altritol, which was purified by silica gel column chromatography (elution: EtOAc/light petroleum, 3/1→1/0, v/v). Yield 74 mg (71%). R_f 0.2 (Et_2O). $[\alpha]_D^{20}$ +20.6 (c 0.5). ^1H NMR: δ 7.34-7.25 (m, 10H, H-arom), 5.33 (AB, 2H, CH_2, Bn, J -11.8 Hz), 5.30 (d, 2H, CH_2, Bn, J -0.4 Hz), 4.77-3.80 (m, 6H, H-1, H-2, H-3, H-4, H-5), 3.57 (m, 1H, H-3), 2.51 (m, 1H, OH), 1.88 (m, 1H, OH). $^{13}C\{^1H\}$ NMR: δ 137.7, 137.4 (Cq, arom), 128.5-127.7 (CH, arom), 81.2, 80.2, 78.5, 77.9 (C-2, C-3, C-4, C-5), 73.3, 72.8 (CH_2, Bn), 62.2 (C-1, C-6).
Hydrogenation of 2,5-anhydro-3,4-di-*O*-benzyl-D-altritol (49 mg, 0.14 mmol) as described in the general procedure gave **8b**. Yield 32 mg (90%).

*H_2SO_4-mediated cyclization of **13b*** - Cyclization of **13b** (0.33 g, 0.68 mmol) in the presence of H_2SO_4 was performed as described above, to give **14b** and **16b** as an intractable mixture (ratio 1:20) after purification. Yield 0.23 g (73%). R_f 0.5 (Et_2O). $[\alpha]_D^{20}$ -7.1 (c 2). Compound **16b**: ^1H NMR: δ 7.53-7.25 (m, 15H, H-arom), 4.52 (d, 2H, CH_2, Bn, J -1.1 Hz), 4.48 (AB, 2H, CH_2, Bn, J -11.8 Hz), 4.18 (dt, 1H, H-2, $J_{1a,2}$ $J_{2,3}$ 5.2 Hz, $J_{1b,2}$ 9.6 Hz), 3.95 (dt, 1H, H-5, $J_{4,5}$ $J_{5,6a}$ 5.5 Hz, $J_{5,6b}$ 4.4 Hz), 3.85 (t, 1H, H-4, $J_{3,4}$ 5.5 Hz), 3.62 (ddd, 1H, H-6a, $J_{6a,6b}$ -10.3 Hz), 3.45 (t, 1H, H-3, $J_{3,4}$ 5.1 Hz), 3.39 (m, 1H, H-6b), 1.35 (dd, 1H, OH, J 4.7, 8.4 Hz), 1.12 (dd, 1H, H-1a, $J_{1a,1b}$ -14.4 Hz), 0.97 (dd, 1H, H-1b), 0.33, 0.30 (2x s, 6H, $SiCH_3$). $^{13}C\{^1H\}$ NMR: δ 139.1, 137.6 (Cq, arom), 133.3, 128.6-127.5 (CH, arom), 83.4, 81.6, 79.3, 76.6 (C-2, C-3, C-4, C-5), 71.9, 71.8 (CH_2, Bn), 62.2 (C-6), 22.0 (C-1), -2.5 ($SiCH_3$). Further elution gave olefin **15b**. Yield 34 mg (15%).

*Oxidative demasking of **16b** and **14b*** - Treatment of the mixture of **16b** and **14b** (0.23 g, 0.73 mmol, ratio 20:1) with KBr and AcOOH was executed as described in the general procedure to give 2,5-anhydro-3,4-di-*O*-benzyl-D-allitol and 2,5-anhydro-3,4-di-*O*-benzyl-D-altritol after silica gel column chromatography. Yield 49 mg (69%). R_f 0.3 (Et_2O). ^1H NMR, *allo*-isomer: δ 7.34-7.26 (m, 10H, H-arom), 4.60 (AB, 4H, CH_2, Bn, J -12.0 Hz), 4.13 (m, 2H, H-2, H-5), 4.01 (dd, 2H, H-3, H-4, $J_{3,4}$ 3.7 Hz, $J_{2,3}$ $J_{4,5}$ 1.1 Hz), 3.83 (dd, 2H, H-1a, $J_{1a,1b}$ $J_{6a,6b}$ -12.0 Hz, $J_{1a,2}$ $J_{5,6a}$ 2.8 Hz), 3.57 (dd, 2H, H-1b, H-6b, $J_{1b,2}$ $J_{5,6b}$ 3.0 Hz), 2.40 (m, 1H, OH). $^{13}C\{^1H\}$ NMR, *allo*-isomer: δ 137.7 (Cq, arom), 128.3, 127.8, 127.7 (CH, arom), 82.3, 77.3 (C-2, C-3, C-4, C-5), 72.1 (CH_2, Bn), 62.1 (C-1).
Hydrogenation of 2,5-anhydro-3,4-di-*O*-benzyl-D-allitol (49 mg, 0.14 mmol) gave **10b**. Yield 18 mg (77%).

2,3-Di-*O*-benzyl-D-xylose diethyl dithioacetal (17c) - Compound **11c** (14.8 gr, 31.1 mmol) was deacetonated as decribed in the general procedure to give crude **17c**[40] after purification. Yield 11.8 g (87%).

4,5-Di-*O*-benzoyl-2,3-di-*O*-benzyl-D-xylose diethyl dithioacetal (18c) - To a cooled (0°C) solution of crude diol **17c** (7.46 gr, 17.1 mmol) in pyridine (150 mL) was added benzoyl chloride (4.57 mL, 39.3 mmol). Stirring was continued at rt for 3 h, the mixture was concentrated and the residue partitioned between Et_2O (300 mL) and H_2O (50 mL). The organic layer was washed with

H_2O (30 mL), separated and dried ($MgSO_4$). After filtration, solvents were evaporated and the residue purified by silica gel column chromatography (elution: Et_2O/light petroleum, 1/3→1/2, v/v). Yield 10.21 g (93%). R_f 0.4 (Et_2O/light petroleum, 1/1, v/v). $[\alpha]_D^{20}$ +40.5 (c 2). ^1H NMR: δ 8.04-7.90 (m, 4H, H-arom), 7.52-7.24 (m, 16H, H-arom), 5.76 (dt, 1H, H-4, $J_{3,4}$ $J_{4,5a}$ 4.0 Hz, $J_{4,5b}$ 6.8 Hz), 4.73 (AB, 2H, CH_2, Bn, J -11.2 Hz), 4.65 (AB, 2H, CH_2, Bn, J -12.1 Hz), 4.60 (dd, 1H, H-5a, $J_{5a,5b}$ -11.7 Hz), 4.57 (dd, 1H, H-5b), 4.16 (dd, 1H, H-3, $J_{3,4}$ 3.7 Hz), 4.01 (d, 1H, H-1, $J_{1,2}$ 3.6 Hz), 3.91 (dd, 1H, H-2, $J_{2,3}$ 7.0 Hz). $^{13}C\{^1H\}$ NMR: δ 165.8, 165.6 (C=O), 139.6, 137.8, 137.6 (Cq, arom), 133.6-127.6 (CH, arom), 83.0, 77.2, 71.5 (C-2, C-3, C-4), 74.0, 73.5 (CH_2, Bn), 63.2 (C-5), 52.7 (C-1), 25.6, 25.0 (CH_2, SEt), 14.2 (CH_3, SEt).

5,6-Di-*O*-benzoyl-3,4-di-*O*-benzoyl-1-deoxy-1-dimethylphenylsilyl-D-iditol (19c) - The aldehyde obtained from hydrolysis of **18c** (3.64 g, 5.65 mmol) in THF was treated with **1** according to the general procedure for open-chain aldehydes. The oil obtained after extraction was applied onto a column of silica gel and elution was effected with Et_2O/light petroleum (1/3→1/2, v/v) to afford **19c** as an oil. Yield 2.76 g (71%). R_f 0.8 (Et_2O/light petroleum, 3/1, v/v). $[\alpha]_D^{20}$ +26.7 (c 2). ^1H NMR: δ 8.08-7.90 (m, 4H, H-arom), 7.57-7.24 (m, 21H, H-arom), 5.78 (dt, 1H, H-5, $J_{4,5}$ $J_{5,6a}$ 5.4 Hz, $J_{5,6b}$ 6.0 Hz), 4.72 (AB, 2H, CH_2, Bn, J -11.3 Hz), 4.65 (AB, 2H, CH_2, Bn, J -12.2 Hz), 4.59-4.44 (m, 2H, H-6), 4.03 (dd, 1H, H-4, $J_{3,4}$ 6.1 Hz), 3.98 (m, 1H, H-2), 3.39 (dd, 1H, H-3, $J_{2,3}$ 2.4 Hz), 2.01 (d, 1H, OH, J 6.7 Hz), 1.14 (dd, 1H, H-1a, $J_{1a,1b}$ -14.4 Hz, $J_{1a,2}$ 9.6 Hz), 0.93 (dd, 1H, H-1b, $J_{1b,2}$ 4.5 Hz), 0.34, 0.29 (2x s, 6H, $SiCH_3$). $^{13}C\{^1H\}$ NMR: δ 165.6 (C=O), 140.0, 137.8, 137.6 (Cq, arom), 133.6-127.6 (CH, arom), 83.0, 77.2 (C-3, C-4), 74.7, 74.4 (CH_2, Bn), 71.3, 68.5 (C-2, C-5), 63.5 (C-6), 22.2 (C-1), -2.1, -2.9 ($SiCH_3$).

3,4-Di-*O*-benzyl-1-deoxy-1-dimethylphenylsilyl-D-iditol (13c) - Compound **19c** (6.32 g, 9.19 mmol) was dissolved in MeOH (80 mL) and KO*t*-Bu (0.21 g, 1.84 mmol) was added. The mixture was stirred for 16 h, neutralized with Dowex-H^+, filtered and concentrated *in vacuo*. The residual oil was applied onto a column of silica gel and elution was effected with Et_2O/light petroleum (1/1→2/1, v/v) to give **13c** as an oil. Yield 3.84 g (87%). R_f 0.1 (Et_2O/light petroleum, 3/1, v/v). $[\alpha]_D^{20}$ -13.6 (c 1). ^1H NMR: δ 7.53-7.18 (m, 15H, H-arom), 4.55 (AB, 2H, CH_2, Bn, J -10.5 Hz), 4.51 (AB, 2H, CH_2, Bn, J -11.5 Hz), 4.07 (ddd, 1H, H-2, $J_{1a,2}$ 9.4 Hz, $J_{1b,2}$ 5.1 Hz, $J_{2,3}$ 0.8 Hz), 3.84 (ddd, 1H, H-5, $J_{4,5}$ 0.9 Hz, $J_{5,6a}$ 6.8 Hz, $J_{5,6b}$ 4.9 Hz), 3.58 (dd, 1H, H-6a, $J_{6a,6b}$ -10.9 Hz), 3.48-3.38 (m, 3H, H-3, H-4, H-5), 1.24 (dd, 1H, H-1a, $J_{1a,1b}$ -14.7 Hz), 0.98 (dd, 1H, H-1b), 0.33, 0.32 (2x s, 6H, $SiCH_3$). $^{13}C\{^1H\}$ NMR: δ 139.3, 137.7, 137.6 (Cq, arom), 133.3, 128.6-127.6 (CH, arom), 81.6, 77.4 (C-3, C-4), 74.0, 73.8 (CH_2, Bn), 69.8, 67.2 (C-2, C-5), 63.7 (C-6), 21.9 (C-1), -2.1, -3.0 ($SiCH_3$).

BF_3·Et_2O-mediated cyclization of 13c - Cyclization of **13c** (0.33 g, 0.69 mmol) was executed as described above to afford 2,5-anhydro-3,4-di-*O*-benzyl-1-deoxy-1-dimethylphenylsilyl-D-iditol (**14c**) as an oil after purification on silica gel (elution: Et_2O/light petroleum, 1/1, v/v). Yield 0.34 g (61%). R_f 0.6 (Et_2O/light petroleum, 3/1, v/v). $[\alpha]_D^{20}$ -12.8 (c 1). ^1H NMR: δ 7.54-7.20 (m, 15H, H-arom), 4.43 (AB, 2H, CH_2, Bn, J -11.8 Hz), 4.31 (AB, 2H, CH_2, Bn, J -11.6 Hz), 4.22 (ddd, 1H, H-2, $J_{1a,2}$ 7.6 Hz, $J_{1b,2}$ 7.3 Hz, $J_{2,3}$ 3.5 Hz), 4.13 (q, 1H, H-5), 4.04 (dd, 1H, H-4, $J_{3,4}$ 1.5 Hz, $J_{4,5}$ 5.3 Hz), 3.77 (dd, 1H, H-6a, $J_{5,6a}$ 5.5 Hz, $J_{6a,6b}$ -11.6 Hz), 3.67 (dd, 1H, H-6b, $J_{5,6b}$ 4.9 Hz), 3.60 (dd, 1H, H-3), 1.32 (dd, 1H, H-1a, $J_{1a,1b}$ -14.3 Hz), 1.19 (dd, 1H, H-1b), 0.33, 0.31 (2x s, 6H, $SiCH_3$). $^{13}C\{^1H\}$ NMR: δ 138.9, 137.8, 137.4 (Cq, arom), 133.5, 128.7-127.3 (CH, arom), 82.9, 82.7 (C-3, C-4), 78.5, 77.5 (C-2, C-5), 72.2, 71.5 (CH_2, Bn), 61.6 (C-6), 15.7 (C-1), -2.2, -2.7 ($SiCH_3$). Further elution with Et_2O/light petroleum (2/1, v/v) afforded 3,4-di-*O*-benzyl-1,2-dideoxy-D-*xylo*-hex-1-enitol (**15c**). Yield 0.14 g (35%). R_f 0.2 (Et_2O/light petroleum, 3/1, v/v). $[\alpha]_D^{20}$ -2.0 (c 1). ^1H

NMR: δ 7.36-7.21 (m, 10H, H-arom), 6.00 (ddd, 1H, H-2, $J_{1a,2}$ 10.9 Hz, $J_{1b,2}$ 16.7 Hz, $J_{2,3}$ 8.5 Hz), 5.46-5.32 (m, 2H, H-1), 4.58 (AB, 2H, CH_2, Bn, J -10.8 Hz), 4.52 (AB, 2H, CH_2, Bn, J -12.0 Hz), 3.85 (ddd, 1H, H-5, $J_{4,5}$ 1.1 Hz, $J_{5,6a}$ 6.8 Hz, $J_{5,6b}$ 4.8 Hz), 3.56 (dd, 1H, H-6a, $J_{6a,6b}$ -10.5 Hz), 3.50-3.40 (m, 3H, H-3, H-4, H-6b). $^{13}C\{^1H\}$ NMR: δ 137.4 (Cq, arom), 134.8 (C-2), 128.4-127.6 (CH, arom), 119.4 (C-1), 81.3, 81.0 (C-3, C-4), 74.7, 70.8 (CH_2, Bn), 71.1 (C-5), 64.0 (C-6).

Oxidative unmasking of ***14c*** - Treatment of **14c** (0.21 g, 0.45 mmol) with KBr and AcOOH was executed as described in the general procedure to give 2,5-anhydro-3,4-di-*O*-benzyl-D-iditol as an oil after work-up and purification by silica gel column chromatography (elution: Et_2O/light petroleum, 1/2, v/v). Yield 0.11 g (73%). R_f 0.2 (Et_2O). $[\alpha]_D^{20}$ -48.2 (c 1). ^1H NMR: δ 7.37-7.25 (m, 10H, H-arom), 4.56 (s, 2H, CH_2, Bn), 4.50 (AB, 2H, CH_2, Bn, J -12.2 Hz), 4.05-3.95 (m, 1H, H-2), 3.91-3.36 (m, 7H, H-1, H-3, H-4, H-5, H-6), 2.10 (bs, 1H, OH), 1.73 (bs, 1H, OH). $^{13}C\{^1H\}$ NMR: δ 137.4, 137.2 (Cq, arom), 128.6-127.8 (CH, arom), 74.7, 73.4 (C-3, C-4, C-5), 72.9, 72.6 (CH_2, Bn), 66.7 (C-1), 64.6 (C-2), 62.3 (C-6).
Hydrogenation of 2,5-anhydro-3,4-di-*O*-benzyl-D-iditol (0.11 g, 0.32 mmol) gave **8c**. Yield 49 mg (93%).

H_2SO_4-mediated cyclization of ***13c*** - Cyclization of **13c** (0.43 g, 0.90 mmol) in the presence of H_2SO_4 was performed as described above, to give **14c** and 2,5-anhydro-3,4-di-*O*-benzyl-1-deoxy-1-dimethylphenylsilyl-D-gulitol (**16c**) as an intractable mixture (ratio 2:3) after purification. Yield 0.10 g (25%). Compound **16c**: $^{13}C\{^1H\}$ NMR: δ 138.5, 138.1 (Cq, arom), 133.5, 128.4-127.3 (CH, arom), 83.8, 81.0 (C-3, C-4), 77.5, 77.3 (C-2, C-5), 73.3, 72.1 (CH_2, Bn), 61.6 (C-6), 18.9 (C-1), -2.0, -2.6 ($SiCH_3$). Olefin **15c** was isolated as the major product. Yield 0.18 g (61%).

Oxidative unmasking of ***14c*** *and* ***16c*** - Treatment of the mixture of **14c** and **16c** (0.10 g, 0.22 mmol, ratio 1:2) with KBr and AcOOH was executed as described in the general procedure to give 2,5-anhydro-3,4-di-*O*-benzyl-D-iditol as an oil after work-up and silica gel column chromatography (elution: Et_2O/light petroleum, 1/3, v/v). Yield 22 mg (29%). Further elution with Et_2O afforded the 2,5-anhydro-3,4-di-*O*-benzyl-D-gulitol. Yield 33 mg (44%). R_f 0.1 (Et_2O). $[\alpha]_D^{20}$ -35.5 (c 1). ^1H NMR: δ 7.35-7.25 (m, 15H, H-arom), 4.57 (AB, 2H, CH_2, Bn, J -12.0 Hz), 4.53 (AB, 2H, CH_2, Bn, J -11.8 Hz), 4.48 (AB, 2H, CH_2, Bn, J -12.0 Hz), 4.35, 4.33 (2x dd, H-2, H-5), 4.05, 3.98 (2x d, 2H, H-3, H-4), 3.75-3.68 (m, 4H, H-1, H-6), 2.27 (bs, 1H, OH). $^{13}C\{^1H\}$ NMR: δ 138.0, 137.7, 137.3 (Cq, arom), 128.5-127.5 (CH, arom), 84.5, 82.8, 82.3, 80.0 (C-2, C-3, C-4, C-5), 73.5, 71.9, 71.6 (CH_2, Bn), 68.2 (C-6), 63.0 (C-1).
Hydrogenation of 2,5-anhydro-3,4-di-*O*-benzyl-D-gulitol (33 mg, 0.10 mmol) gave **10c**. Yield 15 mg (97%).

2,3,5-Tri-*O*-benzyl-D-*arabinono*-1,4-lactone (20) - Compound **2a** (2.50 g, 6.0 mmol) was dissolved in DMSO (20 mL) and Ac_2O (10 mL) was added. The mixture was stirred at rt for 14 h, after which time TLC analysis (Et_2O/light petroleum, 3/1, v/v) indicated the presence of a single product (R_f 0.8). The mixture was diluted with 30 mL of ice-cold H_2O and stirred for 1 h. The precipitate was filtered out, washed with H_2O (10 mL) crystallized from Et_2O/light petroleum to afford **20** as white needles. Yield 2.28 g (92%). R_f 0.8 (Et_2O/light petroleum, 3/1, v/v). Mp 64-66°C (Lit.[26] 67.5-68.5°C). $[\alpha]_D^{20}$ +5.9 (c 1) (Lit.[26] +6.6). ^1H NMR: δ 7.37-7.14 (m, 15H, H-arom), 4.91 (AB, 2H, CH_2, Bn, J -11.4 Hz), 4.58 (AB, 2H, CH_2, Bn, J -11.5 Hz), 4.33 (s, 2H, CH_2, Bn), 4.54-4.48 (m, 3H, H-2, H-3, H-4), 3.73 (dd, 1H, H-5a, $J_{4,5a}$ 2.1 Hz, $J_{5a,5b}$ -11.9 Hz), 3.59 (dd, 1H, H-5b, $J_{4,5b}$ 3.0 Hz). $^{13}C\{^1H\}$ NMR: δ 172.0 (C-1), 137.2, 136.8, 136.5 (Cq, arom), 128.0-127.2 (CH, arom), 78.8, 78.6, 78.3 (C-2, C-3, C-4), 72.8, 72.0, 71.9 (CH_2, Bn), 67.5 (C-5).

3,4,6-Tri-*O*-benzyl-1-deoxy-D-*arabino*-2-hexulofuranose (21) - To a stirred solution of compound **20** (0.83 g, 2.0 mmol) in THF (8 mL) at -78°C was added dropwise a solution of MeLi in Et_2O (1.38 mL, 1.6 M). After the addition was complete and the mixture was stirred an additional 30 min, TLC analysis (Et_2O/light petroleum, 3/1, v/v) indicated the disappearance of **20** and the formation of a more hydrophilic product (R_f 0.6). MeOH (1 mL) was added and the mixture was allowed to warm to rt. The mixture was partitioned between Et_2O (60 mL) and H_2O (30 mL), the organic layer was separated, washed with H_2O (20 mL), and dried ($MgSO_4$). Removal of solvent under reduced pressure and purification of the residue on silica gel by elution with Et_2O/light petroleum (3/2, v/v) afforded **21** as a mixture of anomers. Yield 0.81 g (94%). R_f 0.6 (Et_2O/light petroleum, 3/1, v/v). ^1H NMR: δ 7.30-7.16 (m, 15H, H-arom), 4.74-4.43 (m, 6H, CH_2, Bn), 4.17-4.08 (m, 2H, H-3, H-4), 3.86 (d, 1H, H-3, $J_{3,4}$ 4.8 Hz), 3.62-3.47 (m, 2H, H-6), 1.51, 1.49 (2x s, CH_3). $^{13}C\{^1H\}$ NMR: δ 127.5-127.1 (Cq, arom), 128.2-127.4 (CH, arom), 106.3, 102.2 (C-2), 87.1, 86.1, 83.3, 82.6, 81.1, 79.7 (C-3, C-4, C-5), 73.3, 73.0, 72.3, 71.9, 71.5, 70.7, 70.1 (CH_2, Bn, C-6), 25.1, 21.5 (C-1).

3,4,6-Tri-*O*-benzyl-1-deoxy-1-dimethylphenylsilyl-2-*C*-methyl-D-glucitol (22) - Compound **21** (0.30 g, 0.7 mmol) was treated with the Grignard reagent **1** (3 equiv.) as described in the general procedure to afford homogeneous **22**, along with a minor amount of unreacted **21**, after 14 h stirring at 60°C, work-up and silica gel column chromatography. Yield 0.29 g (71%). R_f 0.8 (Et_2O/light petroleum, 3/1, v/v). $[\alpha]_D^{20}$ 16.5 (c 0.5). ^1H NMR: δ 7.59-7.22 (m, 20H, H-arom), 4.66 (AB, 2H, CH_2, Bn, *J* -11.3 Hz), 4.58 (AB, 2H, CH_2, Bn, *J* -11.4 Hz), 4.52 (s, 2H, CH_2, Bn), 3.96 (m, 1H, H-5), 3.79 (dd, 1H, H-4, $J_{3,4}$ 4.5 Hz), 3.65 (dd, 1H, H-6a, $J_{5,6a}$ 3.4 Hz, $J_{6a,6b}$ -9.8 Hz), 3.59 (dd, 1H, H-6b, $J_{5,6b}$ 5.8 Hz), 3.47 (d, 1H, H-3), 2.87, 2.72 (2x bs, 2H, OH), 1.38 (d, 1H, H-1a, $J_{1a,1b}$ -14.5 Hz), 1.27 (s, 3H, CH_3), 1.21 (d, 1H, H-1b), 0.37, 0.35 (2x s, 6H, $SiCH_3$). $^{13}C\{^1H\}$ NMR: δ 140.2, 138.3, 138.1, 137.6 (Cq, arom), 133.6-127.3 (CH, arom), 86.2, 78.3 (C-3, C-4), 75.4, 75.0, 73.4, 73.2 (CH_2, Bn, C-2), 71.2 (C-6), 71.5 (C-5), 27.3 (C-1), -0.8, -0.9 ($SiCH_3$).

BF_3·Et_2O-mediated cyclization of 22 - Treatment of **22** (0.15 g, 0.26 mmol) with BF_3·Et_2O as described in the general procedure afforded 2,5-anhydro-3,4,6-tri-*O*-benzyl-1-deoxy-1-dimethylphenylsilyl-2-*C*-methyl-D-glucitol (**23**) after work-up and purification by silica gel column chromatography (elution: Et_2O/light petroleum, 1/3, v/v). Yield 35 mg (24%). R_f 0.8 (Et_2O/light petroleum, 1/1, v/v). ^1H NMR: δ 7.63-7.16 (m, 20H, H-arom), 4.51 (s, 2H, CH_2, Bn), 4.50 (AB, 2H, CH_2, Bn, *J* -12.0 Hz), 4.46 (AB, 2H, CH_2, Bn, *J* -11.9 Hz), 4.10 (ddd, 1H, H-5), 4.02 (dd, 1H, H-4, $J_{3,4}$ 3.0 Hz, $J_{4,5}$ 5.2 Hz), 3.73 (dd, 1H, H-6a, $J_{5,6a}$ 6.1 Hz, $J_{6a,6b}$ -9.8 Hz), 3.62 (d, 1H, H-3), 3.53 (dd, 1H, H-6b, $J_{5,6b}$ 5.6 Hz), 1.53 (d, 1H, H-1a, $J_{1a,1b}$ -14.8 Hz), 1.31 (s, 3H, CH_3, Me), 1.20 (d, 1H, H-1b), 0.35, 0.34 (2x s, 6H, $SiCH_3$). ^1H NMR (nOe): A nOe-DIFF resonance was observed at H-3 (δ 3.62) and H-4 (δ 4.02) after irradiation at Me (δ 1.31) and H-1a (δ 1.53), respectively. $^{13}C\{^1H\}$ NMR: δ 138.2, 138.1, 137.8 (Cq, arom), 133.6, 128.7-127.3 (CH, arom), 89.2, 85.0 (C-3, C-4), 79.8 (C-5), 73.3, 71.8, 71.4, 71.0 (CH_2, Bn, C-6), 26.3 (CH_3, Me), 24.4 (C-1), -2.4, -2.9 ($SiCH_3$).

Further elution (Et_2O/light petroleum, 1/2, v/v) afforded 3,4,6-tri-*O*-benzyl-1,2-dideoxy-2-*C*-methyl-D-*arabino*-hex-1-enitol (**24**). Yield 71 mg (64%). R_f 0.5 (Et_2O/light petroleum, 1/1, v/v). ^1H NMR: δ 7.33-7.21 (m, 15H, H-arom), 5.16 (s, 2H, H-1), 4.65 (AB, 2H, CH_2, Bn, *J* -11.2 Hz), 4.46 (s, 2H, CH_2, Bn), 4.45 (AB, 2H, CH_2, Bn, *J* -12.3 Hz), 4.22 (d, 1H, H-3, $J_{3,4}$ 4.6 Hz), 4.00 (m, 1H, H-5), 3.68 (dd, 1H, H-4, $J_{4,5}$ 6.8 Hz), 3.66 (d, 2H, H-6, $J_{5,6}$ 3.9 Hz), 2.80 (bs, 1H, OH). $^{13}C\{^1H\}$ NMR: δ 141.9 (C-2), 138.1, 137.8 (Cq, arom), 128.3-127.5 (CH, arom), 115.0 (C-1), 82.8, 80.7 (C-3, C-4), 74.6, 73.2, 70.8, 70.6 (CH_2, Bn, C-6), 70.4 (C-5), 18.7 (CH_3, Me).

General procedure for the preparation of substituted phenylsilanes 26a + 26b - A phenylbromide **25** (2.25 g, 10 mmol) was dissolved in dry Et_2O (50 mL) and cooled to 0°C. A solution of *n*-BuLi in hexanes (16.0 mL, 1.6 M) was added dropwise, the resulting solution was stirred for 1 h and chloro(chloromethyl)dimethylsilane (1.32 mL, 10 mmol) was added. The mixture was stirred for 15 min, quenched with brine (10 mL) and the layers were separated. The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was applied onto a column of silica gel and elution effected with light petroleum to give silane **26**.

(Chloromethyl)dimethyl(*o*-trifluoromethylphenyl)silane (26a). Yield 2.53 g (88%). R_f 0.6 (light petroleum). $^{13}C\{^1H\}$ NMR: δ 136.3, 130.9, 129.7, 126.2 (CH, arom), 127.7, 122.6 (Cq, arom), 30.5 ($SiCH_2Cl$), -3.0 ($SiCH_3$).

(Chloromethyl)dimethyl(*m*-trifluoromethylphenyl)silane (26b). Yield 2.10 g (83%). R_f 0.6 (light petroleum). $^{13}C\{^1H\}$ NMR: δ 137.5 (Cq, arom), 137.0, 130.0, 128.1, 126.2 (CH, arom), 121.5 (Cq, arom), 30.5 ($SiCH_2Cl$), -3.0 ($SiCH_3$).

3,4,6-Tri-*O*-benzyl-1-deoxy-1-dimethyl(*o*-trifluoromethylphenyl)silyl-D-glucitol (28a) - Compound **2a** (0.84 g, 2.0 mmol) was treated with **27a**, obtained by metallation of **26a** (1.26 g, 5.0 mmol) with magnesium as in the preparation of **1**, according to the general procedure. The oil obtained after extraction was applied onto a column of silica gel and elution was effected with Et_2O/light petroleum (1/2→1/1, v/v) to give **28a** as an oil. Yield 0.94 g (73%). R_f 0.6 (toluene/EtOAc, 3/2, v/v). ^1H NMR: δ 7.77-7.18 (m, 19H, H-arom), 4.62 (AB, 2H, CH_2, Bn, *J* -11.2 Hz), 4.51, 4.48 (2x s, 4H, CH_2, Bn), 4.14-3.95 (m, 2H, H-2, H-5), 3.71-3.60 (m, 3H, H-4, H-6), 3.40 (t, 1H, H-3), 2.93 (d, 1H, OH, *J* 5.6 Hz), 2.33 (d, 1H, OH, *J* 7.4 Hz), 1.19 (dd, 1H, H-1a, $J_{1a,1b}$ -14.8 Hz, $J_{1a,2}$ 9.5 Hz), 0.94 (dd, 1H, H-1b, $J_{1b,2}$ 4.5 Hz), 0.40, 0.38 (2x s, 6H, $SiCH_3$). $^{13}C\{^1H\}$ NMR: δ 137.9 (Cq, arom), 136.2, 130.5-125.8 (CH, arom), 84.4, 78.2 (C-3, C-4), 74.7, 73.5, 73.2 (CH_2, Bn), 71.0 (C-6), 70.7, 68.6 (C-2, C-5), 22.0 (C-1), -2.1, -2.8 ($SiCH_3$).

3,4,6-Tri-*O*-benzyl-1-deoxy-1-dimethyl(*m*-trifluoromethylphenyl)silyl-D-glucitol (28b) - Prepared as described for the preparation of **28a**. Yield 1.24 g (97%). R_f 0.7 (toluene/EtOAc, 3/2, v/v). ^1H NMR: δ 7.72-7.15 (m, 19H, H-arom), 4.64 (AB, 2H, CH_2, Bn, *J* -11.3 Hz), 4.52, 4.51 (2x s, 4H, CH_2, Bn), 4.06-3.92 (m, 2H, H-2, H-5), 3.71-3.58 (m, 3H, H-4, H-6), 3.45 (t, 1H, H-3, $J_{2,3}$ $J_{3,4}$ 4.3 Hz), 1.12 (dd, 1H, H-1a, $J_{1a,1b}$ -14.6 Hz, $J_{1a,2}$ 10.5 Hz), 0.86 (dd, 1H, H-1b, $J_{1b,2}$ 4.0 Hz), 0.38, 0.33 (2x s, 6H, $SiCH_3$). $^{13}C\{^1H\}$ NMR: δ 137.9 (Cq, arom), 137.0, 128.4-125.4 (CH, arom), 84.3, 78.1 (C-3, C-4), 74.8, 73.6, 73.4 (CH_2, Bn), 71.1 (C-6), 70.8, 68.6 (C-2, C-5), 21.5 (C-1), -1.9, -2.6 ($SiCH_3$).

BF_3·Et_2O-mediated cyclization of 28a - Cyclization of compound **28a** (0.47 g, 0.74 mmol) was executed as described in the general procedure. The oil obtained after work-up was applied onto a column of silica gel, which was eluted with Et_2O/light petroleum (1/4→1/3, v/v) to give 2,5-anhydro-3,4,6-tri-*O*-benzyl-1-deoxy-1-dimethyl(*o*-trifluoromethyl)phenylsilyl-D-glucitol (**29a**). Yield 0.25 g (54%). R_f 0.8 (Et_2O/light petroleum, 1/1, v/v). ^1H NMR: δ 7.75-7.19 (m, 19H, H-arom), 4.51 (AB, 2H, CH_2, Bn, *J* -12.0 Hz), 4.47 (AB, 2H, CH_2, Bn, *J* -12.6 Hz), 4.33 (AB, 2H, CH_2, Bn, *J* -12.0 Hz), 4.10 (dt, 1H, H-2, $J_{1a,2}$ $J_{1b,2}$ 7.7 Hz, $J_{2,3}$ 3.5 Hz), 3.93 (m, 1H, H-5), 3.86 (bd, 1H, H-4, $J_{4,5}$ 3.2 Hz), 3.61 (bd, 1H, H-3), 3.58 (dd, 1H, H-6a, $J_{5,6a}$ 5.8 Hz, $J_{6a,6b}$ -10.0 Hz), 3.47 (dd, 1H, H-6b, $J_{5,6b}$ 6.5 Hz), 1.44 (dd, 1H, H-1a, $J_{1a,1b}$ -14.2 Hz), 1.30 (dd, 1H, H-1b), 0.40, 0.39 (2x s, 6H, $SiCH_3$). $^{13}C\{^1H\}$ NMR: δ 138.3, 137.9, 137.8 (Cq, arom), 136.2, 130.5-125.8 (CH, arom), 84.2, 83.9, 82.2, 79.0 (C-2, C-3, C-4, C-5), 73.2, 71.3, 71.0, 70.8 (CH_2, Bn, C-6), 15.8 (C-1), -0.4,

-1.3 ($SiCH_3$). Further elution with Et_2O/light petroleum (1/2, v/v) gave **5a**. Yield 85 mg (27%).

BF_3·Et_2O-mediated cyclization of 28b - Cyclization of compound **28b** (0.16 g, 0.25 mmol) and work-up was executed as described in the general procedure. The residual oil was purified by silica gel column chromatography (elution: Et_2O/light petroleum, 1/4→1/3, v/v) to give 2,5-anhydro-3,4,6-tri-*O*-benzyl-1-deoxy-1-dimethyl(*m*-trifluoromethyl)phenylsilyl-D-glucitol (**29b**). Yield 90 mg (58%). R_f 0.8 (Et_2O/light petroleum, 1/1, v/v). ^1H NMR: δ 7.73-7.22 (m, 19H, H-arom), 4.49 (AB, 2H, CH_2, Bn, *J* -12.1 Hz), 4.47 (AB, 2H, CH_2, Bn, *J* -12.1 Hz), 4.20 (AB, 2H, CH_2, Bn, *J* -11.3 Hz), 4.21 (ddd, 1H, H-2, $J_{1a,2}$ 7.1 Hz, $J_{1b,2}$ 8.1 Hz, $J_{2,3}$ 3.3 Hz), 4.00 (m, 1H, H-5), 3.88 (dd, 1H, H-4, $J_{3,4}$ 0.7 Hz, $J_{4,5}$ 3.0 Hz), 3.57 (dd, 1H, H-6a, $J_{5,6a}$ 5.7 Hz, $J_{6a,6b}$ -9.9 Hz), 3.57 (dd, 1H, H-3), 3.43 (dd, 1H, H-6b, $J_{5,6b}$ 6.4 Hz), 1.18 (dd, 1H, H-1a, $J_{1a,1b}$ -14.4 Hz), 1.07 (dd, 1H, H-1b), 0.38, 0.33 (2x s, $SiCH_3$). $^{13}C\{^1H\}$ NMR: δ 139.2, 138.6 (Cq, arom), 137.0, 128.4-125.2 (CH, arom), 84.7, 84.4, 82.3, 79.9 (C-2, C-3, C-4, C-5), 73.8, 72.3, 71.3, 71.0 (CH_2, Bn, C-6), 16.0 (C-1), -1.3, -1.7 ($SiCH_3$). Further elution with Et_2O/light petroleum (1/2, v/v) gave **5a**. Yield 45 mg (43%).

(Chloromethyl)diethylphenylsilane (30a) - To a cooled (0°C) solution of bromobenzene (2.74 mL, 26.0 mmol) in Et_2O (60 mL) under an atmosphere of nitrogen was added dropwise with stirring a solution of *n*-BuLi in hexanes (16.3 mL, 1.6 M) and stirring continued for 1 h. The solution was cooled (-60°C) and there was added all at once dichlorodiethylsilane (3.74 mL, 25 mmol) *via* syringe. After stirring the resulting mixture for 0.5 h, it was allowed to warm to rt and deposited salts, under a stream of argon, were filtered off (Celite). The filtrate was concentrated under reduced pressure and the residue was dissolved in THF (65 mL), bromochloromethane (1.95 mL, 30.0 mmol) was added and the mixture was cooled to -70°C before the slow addition, *via* the cold wall of the flask, of a solution of *n*-BuLi in hexanes (18.8 mL, 1.6 M). Stirring was continued at -65 to -70°C for 1 h, allowed to warm to rt and neutralized by the addition of aqueous NH_4Cl (40 mL, 15%). The mixture was transferred to a separatory funnel, light petroleum (100 mL) was added and the layers were separated. The organic phase washed with brine (30 mL), dried ($MgSO_4$), filtered and concentrated. Purification on silica gel (eluent: light petroleum) afforded **30a** as a liquid. Yield 1.91 g (36%). R_f 0.6 (light petroleum). ^1H NMR: δ 7.55-7.50 (m, 2H, H-arom), 7.41-7.34 (m, 3H, H-arom), 3.06 (s, 2H, $SiCH_2Cl$), 1.09-0.92 (m, 10H, CH_2, CH_3, Et). $^{13}C\{^1H\}$ NMR: δ 134.0, 129.4, 127.8 (CH, arom), 27.2 ($SiCH_2Cl$), 7.01 (CH_3, Et), 2.60 (CH_2, Et).

(Chloromethyl)phenyl(di-*iso*-propyl)silane (30b) - Transmetallation of bromobenzene (2.32 mL, 22.0 mmol) with *n*-BuLi (13.8 mL, 1.6 M), followed by addition of dichloro(di-*iso*-propyl)silane (3.70 g, 20.0 mmol) and treatment of the resulting chlorosilane with chloromethyllithium, prepared *in situ* by treatment of bromochloromethane (1.56 mL, 24.0 mmol) with *n*-BuLi (15.0 mL, 1.6 M) was executed as described for the preparation of **30a**. Purification on silica gel gave pure **30b** as an oil. Yield 3.49 g (72%). R_f 0.6 (light petroleum). ^1H NMR: δ 7.52-7.25 (m, 5H, H-arom), 3.20 (s, 2H, $SiCH_2Cl$), 1.52-1.36 (m, 2H, CH, *i*-Pr), 1.14-0.92 (m, 6H, CH_3, *i*-Pr). $^{13}C\{^1H\}$ NMR: δ 134.7 (CH, arom), 133.8 (Cq, arom), 129.3, 127.8 (CH, arom), 25.5 ($SiCH_2Cl$), 17.8 (CH_3, *i*-Pr), 10.3 (CH, *i*-Pr).

3,4,6-Tri-*O*-benzyl-1-deoxy-1-diethylphenylsilyl-D-glucitol (32a) - Compound **2a** (0.89 g, 2.12 mmol) was treated with **31a**, prepared by metallation of **30a** (1.13 g, 5.30 mmol) as in the preparation of **1**, according to the general procedure. The oil obtained after extraction was applied onto a column of silica gel and elution was effected with Et_2O/light petroleum (1/2→1/1, v/v) to give **32a** as an oil. Yield 1.08 g (85%). R_f 0.7 (toluene/EtOAc, 3/2, v/v). $[\alpha]_D^{20}$ 72.4 (c 1). ^1H NMR: δ 7.51-7.15 (m, 20H, H-arom), 4.59 (AB, 2H, CH_2, Bn, *J* -11.3 Hz), 4.50, 4.49 (2x s, 4H,

CH_2, Bn), 4.09-3.89 (m, 2H, H-2, H-5), 3.72-3.58 (m, 3H, H-4, H-6), 3.44 (t, 1H, H-3), 2.90 (bs, 1H, OH), 2.43 (bs, 1H, OH), 1.14 (dd, 1H, H-1a, $J_{1a,1b}$ -14.5 Hz, $J_{1a,2}$ 9.9 Hz), 1.04-0.82 (m, 11H, H-1b, CH_2, CH_3, Et). $^{13}C\{^1H\}$ NMR: δ 137.9, 137.6, 136.9 (Cq, arom), 133.9, 128.4-127.2 (CH, arom), 83.9, 78.1 (C-3, C-4), 74.2, 73.3, 72.9 (CH_2, Bn), 70.9 (C-6), 70.5, 68.1 (C-2, C-5), 17.9 (C-1), 7.2 (CH_3, Et), 4.1, 3.5 (CH_2, Et).

3,4,6-Tri-*O*-benzyl-1-deoxy-1-phenyl(di-*iso*-propyl)silyl-D-glucitol (32b) - Prepared from **2a** (0.21 g, 0.5 mmol) and **31b** as described for the preparation of **32a**. Yield 0.27 g (88%). R_f 0.8 (toluene/EtOAc, 3/2, v/v). ^1H NMR: δ 7.48-7.21 (m, 20H, H-arom), 4.66 (AB, 2H, CH_2, Bn, *J* -11.3 Hz), 4.56 (AB, 2H, CH_2, Bn, *J* -11.7 Hz), 4.50 (s, 2H, CH_2, Bn), 4.17-3.97 (m, 2H, H-2, H-5), 3.76-3.46 (m, 3H, H-4, H-6), 3.45 (t, 1H, H-3), 1.38-1.20 (m, 3H, H-1a, CH, *i*-Pr), 1.14-0.96 (m, 7H, H-1b, CH_3, *i*-Pr). $^{13}C\{^1H\}$ NMR: δ 138.0, 137.7, 135.6 (Cq, arom), 134.7, 128.5-127.4 (CH, arom), 84.4, 78.3 (C-3, C-4), 74.5, 73.5, 73.2 (CH_2, Bn), 71.0 (C-6), 70.7, 68.0 (C-2, C-5), 18.0 (CH_3, *i*-Pr), 15.9 (C-1), 11.3, 11.0 (CH, *i*-Pr).

BF_3·Et_2O-mediated cyclization of 32a - Cyclization of compound **32a** (0.62 g, 1.03 mmol) was executed as described in the general procedure. The oil obtained after work-up was applied onto a column of silica gel, which was eluted with Et_2O/light petroleum (1/4→1/3, v/v) to give 2,5-anhydro-3,4,6-tri-*O*-benzyl-1-deoxy-1-diethylphenylsilyl-D-glucitol (**33a**) and 2,5-anhydro-3,4,6-tri-*O*-benzyl-1-deoxy-1-diethylfluorosilyl-D-glucitol (**34a**) as an intractable mixture (ratio 5:1). Yield 0.49 g (65%). R_f 0.8 (Et_2O/light petroleum, 1/1, v/v). Compound **33a**: ^1H NMR: 7.52-7.17 (m, 20H, H-arom), 4.51 (AB, 2H, CH_2, Bn, *J* -12.0 Hz), 4.44 (AB, 2H, CH_2, Bn, *J* -11.3 Hz), 4.17 (AB, 2H, CH_2, Bn, *J* -11.8 Hz), 4.12-3.92 (m, 2H, H-2, H-5), 3.81 (d, 1H, H-4, $J_{4,5}$ -3.3 Hz), 3.57 (dd, 1H, H-6a, $J_{5,6a}$ 6.8 Hz, $J_{6a,6b}$ -10.1 Hz), 3.51-3.43 (m, 2H, H-3, H-6b), 1.24 (dd, 1H, H-1a, $J_{1a,1b}$ -14.5 Hz, $J_{1a,2}$ 9.9 Hz), 1.02-0.76 (m, 11H, H-1b, CH_2, CH_3, Et). δ $^{13}C\{^1H\}$ NMR: δ 138.2, 138.1, 137.8, 136.7 (Cq, arom), 134.1, 128.7-127.2 (CH, arom), 84.1, 83.8, 82.0, 78.9 (C-2, C-3, C-4, C-5), 73.1, 71.2, 70.8, 70.6 (CH_2, Bn, C-6), 11.7 (C-1), 7.3 (CH_3, Et), 4.1, 3.6 (CH_2, Et).
Compound **34a**: $^{13}C\{^1H\}$ NMR: δ 138.3, 138.0, 137.5 (Cq, arom), 128.6-127.5 (CH, arom), 84.0, 83.8, 82.2, 77.8 (C-2, C-3, C-4, C-5), 73.5, 71.3, 71.0 (CH_2, Bn, C-6), 13.1 (d, C-1, $J_{F,C}$ 12.1), 7.0, 6.8 (CH_3, Et), 4.5 (d, CH_2, Et, $J_{F,C}$ 4.8 Hz), 4.1 (bd, CH_2, Et). Further elution with Et_2O/light petroleum (1/2, v/v) gave **5a**. Yield 47 mg (11%). Further elution with Et_2O/light petroleum (1/2, v/v) gave **35a**. Yield 35 mg (5%).

BF_3·Et_2O-mediated cyclization of 32b - Cyclization of compound **32b** (0.16 g, 0.25 mmol) was executed as described in the general procedure. The oil obtained after work-up was applied onto a column of silica gel, which was eluted with Et_2O/light petroleum (1/4→1/3, v/v) to give 2,5-anhydro-3,4,6-tri-*O*-benzyl-1-deoxy-1-phenyl(di-*iso*-propyl)silyl-D-glucitol (**33b**) and 2,5-anhydro-3,4,6-tri-*O*-benzyl-1-deoxy-1-fluoro(di-*iso*-propyl)silyl-D-glucitol (**34b**) as an intractable mixture (ratio 1:1). Yield 0.10 g (67%). R_f 0.8 (Et_2O/light petroleum, 1/1, v/v). Compound **33b**: ^1H NMR: δ 7.52-7.23 (m, 20H, H-arom), 4.51 (AB, 2H, CH_2, Bn, *J* -12.0 Hz), 4.45 (AB, 2H, CH_2, Bn, *J* -12.1 Hz), 4.33 (AB, 2H, CH_2, Bn, *J* -11.5 Hz), 4.24 (m, 1H, H-2), 3.99 (ddd, 1H, H-5, $J_{5,6a}$ 5.6 Hz, $J_{5,6b}$ 7.5 Hz, $J_{4,5}$ 3.2 Hz), 3.85 (d, 1H, H-4, $J_{4,5}$ 2.8 Hz), 3.58 (dd, 1H, H-6a, $J_{6a,6b}$ -8.6 Hz), 3.54 (d, 1H, H-3, $J_{2,3}$ 3.2 Hz), 3.49 (dd, 1H, H-6b), 1.50-1.22 (m, 4H, H-1, CH, *i*-Pr), 1.06-0.97 (m, 6H, CH_3, *i*-Pr). $^{13}C\{^1H\}$ NMR: δ 138.2, 138.0, 137.8, 135.3 (Cq, arom), 134.8, 128.5-127.9 (CH, arom), 83.9, 83.7, 82.0, 78.6 (C-2, C-3, C-4, C-5), 73.1, 71.2, 70.8, 70.7 (CH_2, Bn, C-6), 18.1 (CH_3, *i*-Pr), 11.4, 11.0 (CH, *i*-Pr), 9.2 (C-1). Compound **34b**: $^{13}C\{^1H\}$ NMR: δ 138.1, 137.9, 137.7 (Cq, arom), 128.5-127.6 (CH, arom), 84.2, 83.8, 82.2, 77.9 (C-2, C-3, C-4, C-5), 73.2, 71.3, 70.8 (CH_2, Bn, C-6), 16.8, 16.7 (CH_3, *i*-Pr), 12.8 (d, CH, *i*-Pr, $J_{F,C}$ 4.4 Hz), 12.6 (CH, *i*-Pr), 10.5 (d,

C-1, $J_{F,C}$ 13.2 Hz). Further elution with Et_2O/light petroleum (1/2, v/v) gave **35b**. Yield 20 mg (14%). MS (m/z): 551 $[M+H-H_2O]^+$, 569 $[M+H]^+$. $^{13}C\{^1H\}$ NMR: δ 137.9, 137.8 (Cq, arom), 128.4-127.7 (CH, arom), 83.8, 78.1 (C-3, C-4), 74.8, 73.7, 73.4 (CH_2, Bn), 71.1 (C-6), 70.9, 67.4 (C-2, C-5), 17.2 (C-1), 16.8 (CH_3, *i*-Pr), 12.8, 12.5 (CH, *i*-Pr).

*BF_3·Et_2O-mediated cyclization of **36a*** - To a solution of compound **32a** (0.34 g, 0.56 mmol) in acetonitrile (4 mL) was added hexamethyldisilazane (0.36 mL, 1.68 mmol) and TMS-Cl (0.1 mL). After stirring for 1 h, salts were filtered off (Celite) and the filtrated concentrated *in vacuo* to give crude **36a**, which was treated with BF_3·Et_2O as described in the general procedure. Purification on silica gel afforded pure **33a**. Yield 0.27 g (83%). Further elution with Et_2O/light petroleum (1/2, v/v) gave **5a**. Yield 15 mg (7%).

*BF_3·Et_2O-mediated cyclization of **36b*** - Compound **32b** (0.11 g, 0.18 mmol) was silylated as described for the preparation of **36a**, to give crude **36b** after concentration. Cyclization with BF_3·Et_2O was executed as described in the general procedure to give pure **33b**. Yield 0.10 g (90%).

2,5-Anhydro-3,4,6-tri-*O*-benzyl-1-deoxy-1-hydroxy(di-*iso*-propyl)silyl-D-glucitol (38b) - Oxidative unmasking of silane **33b** (0.28 g, 0.45 mmol) was executed as described in the general procedure to give **38b** after silica gel chromatography. Yield 0.13 g (53%). R_f 0.5 (Et_2O/light petroleum, 1/1, v/v). ^1H NMR: δ 7.33-7.18 (m, 15H, H-arom), 4.48 (AB, 2H, CH_2, Bn, *J* -10.8 Hz), 4.45 (s, 2H, CH_2, Bn), 4.30 (AB, 2H, CH_2, Bn, *J* -11.5 Hz), 4.28 (m, 1H, H-2), 3.97 (ddd, 1H, H-5, $J_{5,6a}$ 5.7 Hz, $J_{5,6b}$ 7.6 Hz, $J_{4,5}$ 3.0 Hz), 3.89 (dd, 1H, H-4, $J_{3,4}$ 1.2 Hz, $J_{4,5}$ 3.2 Hz), 3.76 (dd, 1H, H-3, $J_{2,3}$ 3.8 Hz), 3.56 (dd, 1H, H-6a, $J_{6a,6b}$ -8.6 Hz), 3.47 (dd, 1H, H-6b), 2.52 (bs, 1H, OH), 1.27 (dd, 1H, H-1a, $J_{1a,1b}$ -14.5 Hz, $J_{1a,2}$ 9.6 Hz), 1.02-0.90 (m, 6H, CH, CH_3, *i*-Pr), 0.85 (dd, 1H, H-1b, $J_{1b,2}$ 5.8 Hz). $^{13}C\{^1H\}$ NMR: δ 138.2, 138.0, 137.8 (Cq, arom), 128.3-127.3 (CH, arom), 83.8, 83.5, 81.7, 78.9 (C-2, C-3, C-4, C-5), 73.0, 71.2, 71.1, 70.3 (CH_2, Bn, C-6), 17.1 (CH_3, *i*-Pr), 13.2, 12.9 (CH, *i*-Pr), 10.4 (C-1).

2,5-Anhydro-3,4,6-tri-*O*-benzyl-1-deoxy-1-diethylfluorosilyl-D-glucitol (34a) - To a solution of phenylsilane **33a** (0.35 g, 0.61 mmol) in CH_2Cl_2 (3 mL) was added AcOH (73 mg, 1.22 mmol) and BF_3·Et_2O (0.15 mL, 1.22 mmol) and stirring continued for 2 h. The mixture was neutralized by the addition of Et_3N and partitioned between Et_2O (20 mL) and H_2O (5 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residual oil was purified by flash chromatography (elution: Et_2O/light petroleum, 1/1, v/v) to give **34a**. Yield 0.27 g (86%).

2,5-Anhydro-3,4,6-tri-*O*-benzyl-1-deoxy-1-fluoro(di-*iso*-propyl)silyl-D-glucitol (34b) - Compound **33b** (0.19 g, 0.32 mmol) was protodesilylated as described above to give **34b**. Yield 0.17 g (98%).

2,5-Anhydro-3,4,6-tri-*O*-benzyl-D-glucitol (7a) - To a cooled (0°C) solution of *tert*-butyl hydroperoxide (0.50 mL, 90%) in DMF (2.5 mL) was added $CsOH.H_2O$ (0.63 g, 3.84 mmol). After warming to rt, a solution of **34b** (0.17 g, 0.31 mmol) in DMF (1.5 mL) was added dropwise *via* syringe. The reaction mixture was heated to 70°C for 5 h. After cooling to rt, $Na_2S_2O_3$ (0.80 g, 5.06 mmol) was added and the solvent removed *in vacuo*. The resultant oil was partitioned between H_2O (10 mL) and Et_2O (40 mL). The layers were separated and the aqueous layer was extracted with Et_2O (20 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was applied onto a column

of silica gel and elution effected with Et_2O/light petroleum (1/3→1/2, v/v) to give alcohol **7a**. Yield 0.12 g (71%).

H_2SO_4-mediated cyclization of 32a - Cyclization of **32a** (0.73 g, 1.22 mmol) in the presence of H_2SO_4 was performed as described in the general procedure to afford, after work-up and silica gel column chromatography 2,5-anhydro-3,4,6-tri-*O*-benzyl-1-deoxy-1-diethylphenylsilyl-D-mannitol (**37a**) and **33a** as an intractable mixture (ratio 1:1). Yield 0.40 g (56%). Compound **37a**: $^{13}C\{^1H\}$ NMR: δ 139.2, 138.7, 138.5 (Cq, arom), 133.7, 128.5-127.4 (CH, arom), 89.7, 85.8, 81.1, 80.4 (C-2, C-3, C-4, C-5), 73.5, 71.7, 71.4, 70.7 (CH_2, Bn, C-6), 21.3 (C-1), 7.4 (CH_3, Et), 4.3, 3.7 (CH_2, Et).
Olefin **5a** was isolated as a minor product. Yield 76 mg (15%).

H_2SO_4-mediated cyclization of 32b - Cyclization of **32b** (0.58 g, 0.93 mmol) in the presence of H_2SO_4 was performed as described in the general procedure to give, after work-up and silica gel chromatography 2,5-anhydro-3,4,6-tri-*O*-benzyl-1-deoxy-1-phenyl(di-*iso*-propyl)silyl-D-mannitol (**37b**) and **33b** as an intractable mixture (ratio 1:5). Yield 0.23 g (40%). Compound **37b**: $^{13}C\{^1H\}$ NMR: δ 139.4, 138.6, 138.5 (Cq, arom), 134.9, 128.6-127.4 (CH, arom), 89.3, 85.3, 81.1, 80.1 (C-2, C-3, C-4, C-5), 73.2, 72.2, 71.6, 68.7 (CH_2, Bn, C-6), 18.1 (CH_3, *i*-Pr), 16.1 (C-1), -11.3, -10.9 (CH, *i*-Pr).

References and notes

1. Published in part: (a) van Delft, F.L.; van der Marel, G.A.; van Boom, J.H. *Tetrahedron Lett.* **1994**, *35*, 1091. (b) van Delft, F.L.; van der Marel, G.A.; van Boom, J.H. *Recl. Trav. Chim. Pays-Bas* **1994**, *113*, 339.
2. Smid, P.; Noort, D.; Broxterman, H.J.G.; van Straten, N.C.R.; van der Marel, G.A.; van Boom, J.H. *Recl. Trav. Chim. Pays-Bas* **1992**, *111*, 524.
3. Hudrlik, P.F.; Peterson, D. *J. Am. Chem. Soc.* **1975**, *97*, 1464.
4. Formation of tetrahydrofurans: (a) Sugimura, H. *Tetrahedron Lett.* **1990**, *31*, 5909. (b) Veloo, R.A.; Wanner, M.J.; Koomen, G.-J. *Tetrahedron* **1992**, *48*, 5301. (c) Akiyama, T.; Ishikawa, K.; Ozaki, S. *Chem. Lett.* **1994**, 627. (d) Akiyama, T.; Yasusa, T.; Ishikawa, K.; Ozaki, S. *Tetrahedron Lett.* **1994**, *35*, 8401. Formation of isoxazolines: (e) Panek, J.S.; Beresis, R.T. *J. Am. Chem. Soc.* **1993**, *115*, 7898. Formation of pyrrolidines: (f) Kiyooka, S.; Shiomi, Y.; Kira, H.; Kaneko, Y.; Tanimori, S. *J. Org. Chem.* **1994**, *59*, 1958. (g) Panek, J.S.; Jain, N.F. *ibid.* **1994**, *59*, 2674.
5. Whitesell, J.K.; Nabona, K.; Deyo, D. *J. Org. Chem.* **1989**, *54*, 2258.
6. (a) Panek, J.S.; Yang, M. *J. Am. Chem. Soc.* **1991**, *113*, 9868. (b) Panek, J.S.; Beresis, R. *J. Org. Chem.* **1993**, *58*, 809. (c) Panek, J.S.; Cirillo, P.F. *ibid.* **1993**, *58*, 999.
7. (a) Knölker, H.-J.; Jones, P.G.; Pannek, J.-B. *Synlett* **1990**, 429. (b) Imazu, S.; Shimizu, N.; Tsuno, Y. *Chem. Lett.* **1990**, 1845. (c) Snider, B.B.; Zhang, Q. *J. Org. Chem.* **1991**, *56*, 4908. (d) Danheiser, R.L.; Dixon, B.R.; Gleason, R.W. *ibid.* **1992**, *57*, 6094. (e) Ipaktschi, J.; Heydari, A. *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 313. (f) Knölker, H.-J.; Wanzl, G. *Synlett* **1995**, 378.

8. After the appearance of our original manuscripts (reference 1), reports on similar acid-induced cyclization of silanes bearing remote hydroxyl groups have appeared: (a) Adiwidjaja, G.; Flörke, H.; Kirschning, A.; Schaumann, E. *Liebigs Ann. Chem.* **1995**, 501. (b) Miura, K.; Okajima, S.; Hondo, T.; Hosomi, A. *Tetrahedron Lett.* **1995**, *36*, 1483. (c) Adiwidjaja, G.; Flörke, H.; Kirschning, A.; Schaumann, E. *ibid.* **1995**, *36*, 8771. (d) Miura, K.; Hondo, T.; Okajima, S.; Hosomi, A. *ibid.* **1996**, *37*, 487.
9. Freeman, F.; Robarge, K.D. *Carbohydr. Res.* **1987**, *171*, 1.
10. Fleming, I.; Sanderson, P.E.J. *Tetrahedron Lett.* **1987**, *28*, 4229.
11. Collected ^{13}C NMR data of anhydro-hexitols: (a) Que Jr., L.; Gray, G.R. *Biochemistry* **1974**, *13*, 146. (b) Bock, K.; Pedersen, C. *Adv. Carbohydr. Chem.* **1983**, *41*, 27. Further data on 2,5-anhydro-D-glucitol: (c) Koerner, T.A.W.; Voll, R.J.; Younathan, E.S. *Carbohydr. Res.* **1977**, *59*, 403. D-mannitol: (d) Horton, D.; Philips, K.D. *Carbohydr. Res.* **1973**, *30*, 367. (e) Rao, V.S.; Perlin, A.S. *Can. J. Chem.* **1984**, *62*, 886. D-talitol (D-altritol): (f) Defaye, J. *Bull. Chem. Soc. Fr.* **1964**, 999. L-iditol: (g) Rafka, R.J.; Morton, B.J. *Carbohydr. Res.* **1994**, *260*, 155, reference 11e.
12. Lambert, J.B.; Emblidge, R.W.; Malany, S. *J. Am. Chem. Soc.* **1993**, *115*, 1317 and references cited therein.
13. Cyclization under the influence of decreased amounts of $BF_3{\cdot}Et_2O$ or using other Lewis acids in all cases proceeded more sluggishly and led to lower amounts of **4a**.
14. The possible transformation of **4a** into **6a** was excluded by quantitative recovery of **4a** after treatment with H_2SO_4 in THF (72 h at 60°C).
15. For a related example of nucleophilic attack to the same surface of a cation from which the silyl group departs, see: Fleming, I.; Ghosh, S.K. *J. Chem. Soc., Chem. Commun.* **1992**, 1777.
16. Barker, R.; Fletcher Jr., H.G. *J. Org. Chem.* **1961**, *26*, 4605.
17. Kawana, M.; Kuzuhara, H.; Emoto, S. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1492.
18. The *syn*- and *anti*-designation of the adducts **3a-c** was based on results earlier obtained for nucleophilic addition of vinylmagnesium bromide to **2a-c**: Boschetti, A.; Nicotra, F.; Panza, L.; Russo, G. *J. Org. Chem.* **1988**, *53*, 4181.
19. Organozinc reagents generally show high *syn*-stereoselectivity in condensation with α-alkoxy aldehydes. For instance, see reference 18.
20. Identification of the 2,5-anhydro-hexitols is especially facile for **10a**, **10b** and **8c** due to the presence of a C_2-axis (**10a**, **8c**) or a plane (**10b**) of symmetry.
21. Kovács, I.; Tóth, Z.; Herczegh, P.; Sztaricskai, F. *Tetrahedron: Asymmetry* **1993**, *4*, 2261.
22. Vedejs, E.; Fuchs, P.L. *J. Org. Chem.* **1971**, *36*, 366.
23. Cyclization to the THF derivative was expected to be favoured over cyclization to the 6-membered ring.
24. The ^{13}C NMR chemical shift of C-1 in 2,3-cis tetrahydrofurans generally appears in higher field (±4 ppm) than in 2,3-trans tetrahydrofurans.
25. A variety of other methods, *i.e.* NBS/2,6-lutidine/CH_3CN/H_2O, $HgCl_2/HgO$, MeI/collidine/acetone/H_2O and $I_2/NaHCO_3$/1,4-dioxane/H_2O was also unsuccessful.

26. (a) Rabinsohn, Y.; Fletcher Jr., H.G. *J. Org. Chem.* **1970**, *32*, 3452. (b) Meng, Q.; Hesse, M. *Helv. Chim. Acta* **1991**, *74*, 445.
27. Jarvie, A.W.P. *Organomet. Chem. Rev. A* **1970**, *6*, 153.
28. Shimizu, N.; Takesue, N.; Yasuhara, S.; Inazu, T. *Chem. Lett.* **1993**, 1807.
29. Due to decreased stabilization of the cationic intermediate by a diminished β-silicon effect. See for instance: Brook, M.A.; Henry, C.; Jueschke, R.; Modi, P. *Synlett* **1993**, 97.
30. Braddock-Wilking, J.; Chiang, M.Y.; Gaspar, P.P. *Organometallics* **1993**, *12*, 197.
31. Petrie, M.A.; Power, P.P.; Rasika Dias, H.V.; Ruhlandt-Senge, K.; Waggoner, K.M.; Wehmschulte, R.J. *Organometallics* **1993**, *12*, 1086.
32. Kobayashi, T.; Pannell, K.H. *Organometallics* **1991**, *10*, 1960.
33. Fleming, I.; Henning, R.; Plaut, H. *J. Chem. Soc., Chem. Commun.* **1984**, 29.
34. Tamao, K.; Kakui, T.; Akita, M.; Iwahara, T.; Kanatani, R.; Yoshida, J.; Kumada, M. *Tetrahedron* **1983**, *39*, 983.
35. (a) Palomo, C.; Aizpurua, J.M.; Urchegui, R.; Iturburu, M. *J. Org. Chem.* **1992**, *57*, 1571. (b) Sieburth, S.M.; Fensterbank, L. *ibid.* **1992**, *57*, 5279. (c) Winter, E.; Brückner, R. *Synlett* **1994**, 1049. (d) Clive, D.L.J.; Cantin, M. *J. Chem. Soc., Chem. Commun.* **1995**, 319. (e) Barbero, A.; Cuadrado, P.; Fleming, I.; González, A.M.; Pulido, F.J.; Sanchez, A. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1525.
36. Bodnar, P.M.; Palmer, W.S.; Shaw, J.T.; Smitrovich, J.H.; Sonnenberg, J.B.; Presley, A.L.; Woerpel, K.A. *J. Am. Chem. Soc.* **1995**, *117*, 10575.
37. (a) Boivin, T.L.B. *Tetrahedron* **1987**, *43*, 3309. (b) Harmange, J.-C.; Figadère, B. *Tetrahedron: Asymmetry* **1993**, *4*, 1711.
38. (a) Postema, M.H.D. *Tetrahedron* **1992**, *48*, 8545. (b) Buchanan, J.G. in *Progress in the Chemistry of Organic Natural Products*, Vol. 44, Herz, W.; Grisebach, H.; Kirby, G.W. Eds., Springer-Verlag, Wien-New York, 1983. (c) Garner, P. in *Studies in Natural Product Chemistry*, Atta-Yr-Rhaman Ed., Elsevier, Amsterdam, 1988, Vol. I, Part A.
39. (a) Fischer, E. *Ber.* **1894**, *27*, 673. (b) Zinner, H. *Chem. Ber.* **1953**, *86*, 495. (c) Rollin, P.; Pougny, J.-R. *Tetrahedron* **1986**, *42*, 3479.
40. Rao, S.P.; Grindley, T.B. *Carbohydr. Res.* **1991**, *218*, 83.

II

Preparation of 2,5-Anhydro-Hexitols (Part II). Intramolecular Nucleophilic Substitution of Cyclic Sulfates[1]

Abstract

Base treatment of cyclic sulfates carrying a remote acetylated hydroxyl function leads predominantly or exclusively to tetrahydrofuran derivatives *via* 5-*exo*-*tet* cyclization.

Introduction

In the last decade, cyclic sulfates have played a significant role as a synthetic tool in organic chemistry[2]. Cyclic sulfates entailing a 5-,6- or 7-membered ring are readily accessible from diols and show high reactivity towards nucleophilic attack, while competing elimination is stereoelectronically unfavorable. Moreover, nucleophilic ring opening of cyclic sulfates generally proceeds with good regioselectivity and normally only one hydroxyl function of a diol precursor is substituted. Earlier reports from this laboratory have shown[3,4] that a variety of natural products could be prepared from carbohydrate derivatives using cyclic sulfate chemistry. For instance, azido glycosides were obtained *via* regioselective diaxial opening of five-membered cyclic sulfates with lithium azide[4a]. Furthermore, cyclic sulfates of 1,4-diols in open chain carbohydrates are key intermediates[4b] *en route* towards the eight-carbon monosaccharide KDO (3-deoxy-D-*manno*-2-octulosonic acid). A similar methodology was also applied[4c] in the assembly of polyhydroxylated pyrrolidines which are promising glucosidase inhibitors.

In contrast to the intermolecular substitution of cyclic sulfates, the intramolecular version of the reaction has to date received scant attention[5]. This Chapter describes the methoxide-mediated cyclization of 2-acetoxy-5,6-cyclic sulfates of carbohydrate derivatives to 2,5-anhydro-hexitols.

Results and discussion

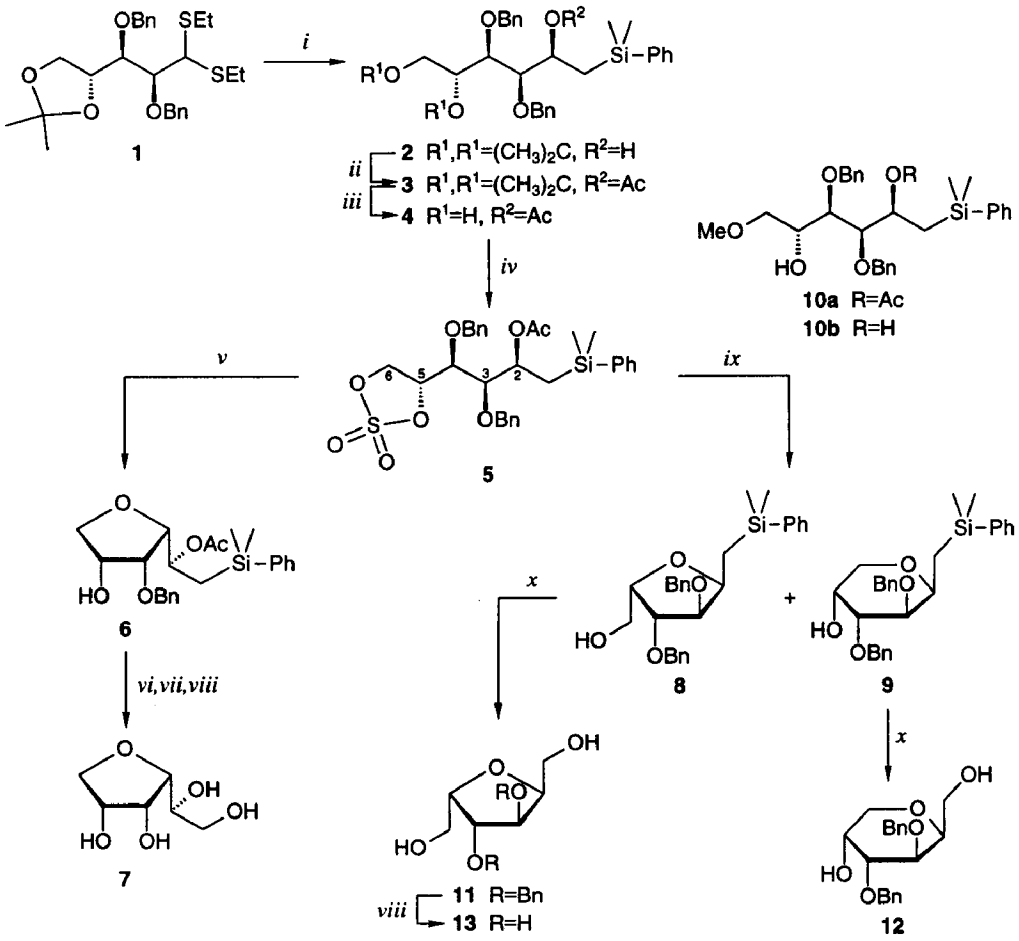
In the previous Chapter it was shown that hydrolysis of dithioacetal **1**, followed by Grignard addition of (dimethylphenylsilyl)methylmagnesium chloride to the resulting aldehyde, produced β-hydroxy silane **2** in excellent yield and stereoselectivity (Scheme 1). Isopropylidene removal of **2** and acid-mediated cyclization of the resulting triol gave, depending on the nature of the acid, 2,5-anhydro hexitols with high stereocontrol[6].

It occurred to us that transformation of **2** into cyclic sulfate **5**, followed by intramolecular cyclization of the latter product, may present an alternative route to 2,5-anhydro hexitols. Cyclization of **5** may proceed under basic conditions *via* intramolecular nucleophilic attack of O-2 at the cyclic sulfate. In this respect, it was expected that 5-*exo-tet* cyclization would predominate.

Acetylation of compound **2** (Ac_2O, pyridine) and subsequent removal of the 5,6-isopropylidene function in **3** with aqueous acetic acid gave diol **4**. Treatment of **4** with thionyl chloride and pyridine in ethyl acetate gave 5,6-cyclic sulfite, which was converted according to Sharpless ($RuCl_3$, $NaIO_4$) into cyclic sulfate **5** (88%). Cyclization of **5** was first investigated under the influence of $NaHCO_3$ in aqueous THF at elevated temperature. Monitoring of the reaction by TLC analysis showed, after 2 h at 20°C, complete conversion of cyclic sulfate **5** into a highly polar compound. Mild acid hydrolysis of the sulfate group at 50°C (16 h) afforded a homogeneous compound (87%), structure analysis of which (^1H and ^{13}C NMR spectroscopy) revealed that the resulting compound was lacking one benzyl group. The latter indicated that debenzylating cycloetherification[5d,7] had taken place *via* nucleophilic attack of the C-3 benzyl oxygen at the primary C-6 position[8], leading to compound **6**. The formation of the tetrahydrofuran derivative **6** was further endorsed by three-step transformation of **6** into 1,4-anhydro-L-gulitol (**7**), ^{13}C NMR data of which were identical with those earlier reported[9] for **7**.

In order to circumvent the debenzylating cycloetherification of **5**, we now turned our attention to the use of methoxide ions. Treatment of compound **5** with K_2CO_3 in a mixture of MeOH and THF[10] resulted in a rapid disappearance (1 h) of the starting material. Unfortunately, subsequent acid hydrolysis led to an intractable mixture of products. On the other hand, a single product was formed (TLC analysis) upon reaction of **5** with potassium methanolate, generated *in situ* by the addition of KO*t*-Bu to the THF/MeOH mixture, and subsequent acid hydrolysis of the sulfate ester. ^{13}C NMR analysis after work-up revealed the presence of two isomeric products **8** and **9** (ratio 5:2), the structures of which were

Scheme 1

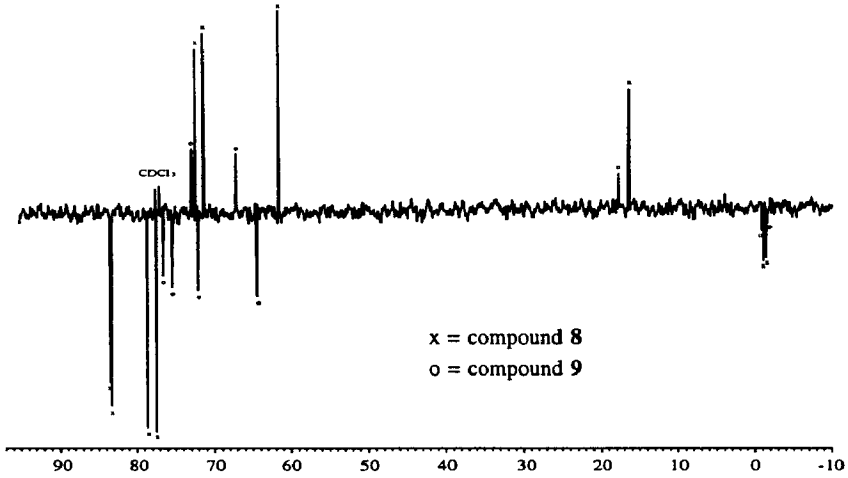


Reagents and conditions

(*i*) (a) HgO, $BF_3{\cdot}Et_2O$, 80% THF (b) $PhMe_2SiCH_2MgCl$, Et_2O, 0°C (90%); (*ii*) Ac_2O, pyridine, 3 h (100%); (*iii*) 80% HOAc, 15 h (91%); (*iv*) (a) $SOCl_2$, pyridine, EtOAc, 0°C, 5 min (b) $RuCl_3$, $NaIO_4$, CH_3CN, CH_2Cl_2, H_2O, 0.5 h (88%); (*v*) (a) $NaHCO_3$, 90% THF, reflux, 2 h (b) H_2SO_4, 50°C, 1 h (87%); (*vi*) KBr, AcO_2H, NaOAc, AcOH, 2 h (64%); (*vii*) KO*t*-Bu, MeOH, 8 h (91%); (*viii*) H_2, Pd-C, 12 h (**7**: 100%, **13**: 96%); (*ix*) (a) LiOMe, MeOH, 3 h (b) H_2SO_4, 50°C, 3 h (**8+9**: 86%, ratio 5:2); (*x*) KBr, NaOAc, AcO_2H, AcOH, 3 h (**11**: 50%, **12**: 21%).

corroborated by comparison of the carbon NMR spectra with those of previously prepared **8** and **9** (preceding Chapter). Moreover, it is of interest to note that the chemical shifts of the ring methine carbons are highly indicative of the ring size, *i.e.* chemical shifts of carbon atoms in a 5-membered ring are generally found downfield from those in a 6-membered ring (Figure 1). The preferential formation of **8** over **9** shows that 5-*exo-tet* cyclization is favored over the corresponding 6-*exo-tet* process. Moreover, side-products

Figure 1. Crude ^{13}C NMR spectrum of the mixture of isomers **8** and **9** resulting from LiOMe treatment of cyclic sulfate **5**.



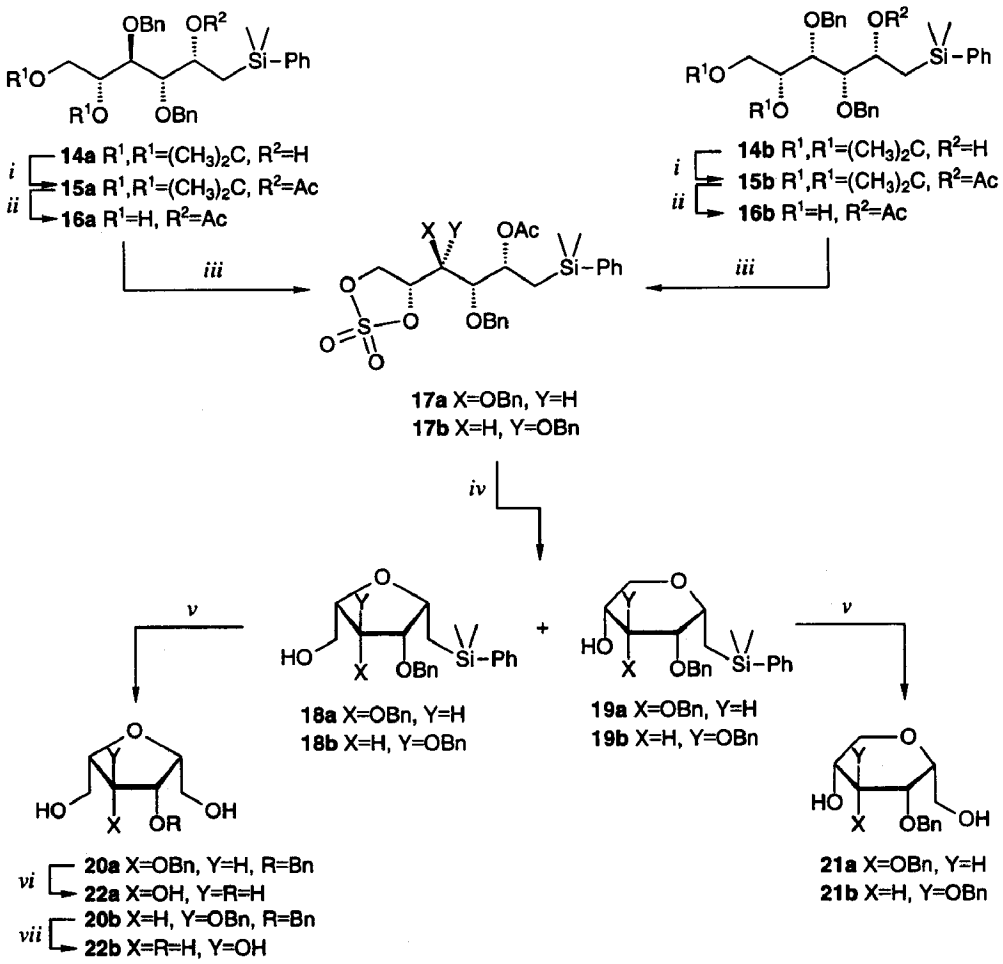
10a or **10b**, resulting from competing attack of the methoxide anion at C-6 of the cyclic sulfate function in **5** were not detected.

In the next stage, improvement of the regioselectivity during cyclization was examined by the application of other methoxide counterions and different solvents. It was established, however, that the nature of the counterion and the polarity of the solvent did not affect the product ratio of **8** and **9**, *i.e.* use of sodium and lithium methoxide in THF/methanol or change of solvent to THF, diethyl ether or DMF showed no variation in regioselectivity. Only a slight increase in yield was observed using LiOMe in THF/methanol.

Oxidative unmasking of the mixture of cyclic products **8** and **9**, followed by separation of the resulting products, led to the isolation of homogeneous alcohols **11** and **12**. Hydrogenolysis of the benzyl protective groups in the major product **11** afforded known[11] 2,5-anhydro-L-iditol (**13**), the spectroscopic data of which were in all aspects identical with an authentic sample[12].

The scope of the intramolecular substitution of cyclic sulfates was further evaluated using the diastereomeric cyclic sulfates **17a** and **17b** (Scheme 2). Thus, β-hydroxy silane adducts **14a** and **14b**, obtained from suitably protected diethyl dithioacetals of D-ribose and D-xylose, respectively (Chapter I), were converted into the corresponding cyclic sulfates by acetylation (Ac_2O, pyridine), deacetonation (80% aqueous HOAc), treatment with thionyl chloride and finally oxidation with $RuCl_3/NaIO_4$. The cyclic sulfates **17a** and **17b** were subjected to LiOMe in MeOH or MeOH/THF[10], respectively. In a similar way as described for arabinose-derived **5**, nucleophilic ring opening of **17a** and **17b** and subsequent acidic hydrolysis resulted in the formation of intractable mixtures of the isomeric products **18a/19a** and **18b/19b**, respectively. In analogy to earlier observations,

Scheme 2



Reagents and conditions

(*i*) Ac_2O, pyridine, 2 h (**15a**: 83%, **15b**: 96%); (*ii*) 80% HOAc, 16 h (**16a**: 83%, **16b**: 92%); (*iii*) (a) $SOCl_2$, pyridine, EtOAc, 0°C (b) $RuCl_3$, $NaIO_4$, CH_3CN, CH_2Cl_2, H_2O (**17a**: 79%, **17b**: 74%); (*iv*) LiOMe, MeOH, 2 h. 2. H_2SO_4, 50°C, 6 h (**18a+19a**: 70%, ratio 6:1, **18b+19b**: 66%, ratio 4:1); (*v*) KBr, AcO_2H, NaOAc, AcOH, 3 h (**20a**: 64%, **21a**: 11%, **20b**: 57%, **21b**: 14%); (*vi*) H_2, Pd-C, MeOH, 10 h (**21a**: 87%, **21b**: 97%).

the 5-membered products **18a,b** are formed preferentially with respect to 6-membered **19a,b** (ratio 6:1 and 4:1 ratio, respectively). Treatment of a mixture of **18a** and **19a** with KBr and peracetic acid resulted in oxidative cleavage of the carbon-silicon bond to give, after separation on silica gel, diastereomerically pure alcohols **20a** and **21a**. Similar oxidative unmasking of **18b** and **19b**, followed by separation, gave homogeneous products **20b** and **21b**. Removal of the benzyl groups in tetrahydrofurans **20a** and **20b** led to a near quantitative isolation[13] of 2,5-anhydro-allitol[14] (**22a**) and 2,5-anhydro-L-glucitol[15] (**22b**).

Conclusion

The intramolecular substitution of cyclic sulfates may be a valuable asset in the future preparation of tetrahydrofuran adducts[16]. In addition, the β-hydroxysilane adducts **2**, **14a** and **14b**, derived from D-arabinose, D-ribose and D-xylose, respectively, are useful precursors for the synthesis of 2,5-anhydro-hexitols (C-glycosides)[17]. In combination with the acid-mediated cyclizations under the influence of $BF_3{\cdot}Et_2O$ or H_2SO_4 (Chapter I), all 2,5-anhydro-hexitols except 2,5-anhydro-L-talitol can be conveniently prepared starting from only three inexpensive pentoses, *i.e.* D-ribose, D-arabinose and L-arabinose.

Experimental

General methods and materials - Toluene was distilled from P_2O_5 and stored over 4Å molecular sieves, THF and Et_2O were freshly distilled from $LiAlH_4$. All reactions were performed under strictly anhydrous conditions unless noted otherwise. Reactions were followed by TLC analysis on Schleicher and Schüll DC Fertigfolien F 1500 LS 254. Compounds were visualized by UV light (254 nm) and spraying with 20% H_2SO_4 in MeOH followed by charring at 140°C. Column chromatography was performed on silica gel 60, 230-400 mesh (Merck). Optical rotations were measured in $CHCl_3$ on a Propol automatic polarimeter. ^1H NMR spectra and ^{13}C NMR spectra (50.1 MHz) were recorded in deuterated chloroform using a Jeol JNM-FX 200 spectrometer. Chemical shifts (δ) are given in ppm relative to tetramethylsilane as internal standard.

2-*O*-Acetyl-3,4-di-*O*-benzyl-5,6-*O*-isopropylidene-1-deoxy-1-dimethylphenylsilyl-D-glucitol (3) - To a stirred solution of compound **2** (3.80 g, 7.31 mmol) in pyridine (30 mL) and Ac_2O (15 mL) was added DMAP (0.1 g). After 3 h, solvents were removed *in vacuo* and the residual oil was coevaporated with 1,4-dioxane (4x 4 mL). The residue was purified on silica gel (elution: Et_2O/light petroleum, 1/4→1/3, v/v) to afford **3** as a solid. Yield 4.10 g (100%). R_f 0.8 (Et_2O/light petroleum, 1/1, v/v). $[\alpha]_D^{20}$ +19.3 (c 1). Mp 56-57°C. ^1H NMR: δ 7.48-7.21 (m, 15H, CH, arom), 5.32 (dt, 1H, H-2, $J_{1a,2}$ $J_{2,3}$ 5.8 Hz, $J_{1b,2}$ 8.3 Hz), 4.68 (AB, 2H, CH_2, Bn, J -11.3 Hz), 4.54 (AB, 2H, CH_2, Bn, J -11.6), 4.15 (dt, 1H, H-5, $J_{4,5}$ 4.7 Hz, $J_{5,6a}$ $J_{5,6b}$ 6.8 Hz), 3.92 (dd, 1H, H-6a, $J_{6a,6b}$ -8.1 Hz), 3.88 (dd, 1H, H-6b), 3.78 (t, 1H, H-4, $J_{3,4}$ 4.7 Hz), 3.43 (dd, 1H, H-3), 1.73 (s, 3H, CH_3, Ac), 1.41, 1.31 (2x s, 6H, CH_3, isoprop), 1.22-1.10 (m, 1H, H-1a), 0.90-0.78 (m, 1H, H-1b), 0.29, 0.24 (2x s, 6H, $SiCH_3$). $^{13}C\{^1H\}$ NMR: δ 169.6 (C=O), 138.2, 138.0 (Cq, arom), 133.3, 128.7-127.3 (CH, arom), 108.2 (Cq, isoprop), 81.8, 78.2, 76.3 (C-3, C-4, C-5), 74.3, 73.6 (CH_2, Bn), 71.2 (C-2), 65.6 (C-6), 26.3, 24.8 (CH_3, isoprop), 20.6 (CH_3, Ac), 17.9 (C-1), -2.6, -3.0 ($SiCH_3$).

2-*O*-Acetyl-3,4-di-*O*-benzyl-1-deoxy-1-dimethylphenylsilyl-D-glucitol (4) - After stirring compound **3** (4.10 g, 7.31 mmol) in 80% aqueous AcOH (80 mL) for 15 h, solvents were removed *in vacuo*, the residue coevaporated with toluene (3x 4 mL) and applied onto a column of silica gel. Elution with Et_2O/light petroleum (1/1→2/1, v/v) afforded compound **4** as an oil. Yield 3.47 g (91%). R_f 0.3 (Et_2O/light petroleum, 3/1, v/v). ^1H NMR: δ 7.52-7.24 (m, 15H, CH, arom), 5.39 (ddd, 1H, H-2, $J_{1a,2}$ 5.8 Hz, $J_{1b,2}$ 8.6 Hz, $J_{2,3}$ 4.7 Hz), 4.56 (AB, 2H, CH_2, Bn, J -11.3 Hz), 4.54 (AB, 2H, CH_2, Bn, J -12.0), 3.70-3.64 (m, 4H, H-4, H-5, H-6), 3.54 (t, 1H, H-3, $J_{3,4}$ 4.7 Hz), 2.94 (bs, 1H, OH), 2.13 (bs, 1H, OH), 1.79 (s, 3H, CH_3, Ac), 1.33 (dd, 1H, H-1a, $J_{1a,1b}$ -14.8 Hz), 0.88-0.82 (m, 1H, H-1b), 0.30, 0.26 (2x s, 6H, $SiCH_3$). $^{13}C\{^1H\}$ NMR: δ 170.1 (C=O), 138.1, 137.6

(Cq, arom), 133.3, 128.7-127.5 (CH, arom), 81.0, 77.5 (C-3, C-4), 73.9, 73.3 (CH_2, Bn), 71.3, 70.8 (C-2, C-5), 63.0 (C-6), 20.7 (CH_3, Ac), 18.3 (C-1), -2.7, -2.9 ($SiCH_3$).

2-*O*-Acetyl-3,4-di-*O*-benzyl-5,6-*O*-(cyclic sulfate)-1-deoxy-1-dimethylphenylsilyl-D-glucitol (5) - To a cooled (0°C) solution of diol **4** (0.78 g, 1.5 mmol) in EtOAc (10 mL) was added $SOCl_2$ (0.20 g, 1.65 mmol) and a mixture of pyridine (0.26 g, 3.30 mmol) and EtOAc (2 mL). After 30 min, TLC-analysis (Et_2O/light petroleum, 1/1, v/v) revealed the conversion of **5** into two more apolar products (R_f 0.7 and 0.8). EtOAc (20 mL) and H_2O (5 mL) were added, the layers separated and the organic layer washed with brine (5 mL). The aqueous phases were combined and extracted with EtOAc (20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was coevaporated with MeCN to remove traces of pyridine before dissolving in a mixture of MeCN (4 mL), CH_2Cl_2 (4 mL) and H_2O (6 mL). To the rapidly stirred mixture was added $NaIO_4$ (0.64 g, 3.0 mmol) and catalytic $RuCl_3$. After 15 min, the mixture was filtered, rinsed with CH_2Cl_2 (20 mL), washed with cold H_2O (5 mL) and dried ($MgSO_4$). The oil obtained after concentration was purified by flash chromatography (elution: CH_2Cl_2/light petroleum, 3/2, v/v) to give **5** as white crystals. Yield 0.76 g (88%). R_f 0.5 (Et_2O/light petroleum, 1/1, v/v). $[\alpha]_D^{20}$ +9.0 (c 1). Mp 97-98°C (decomp). ^1H NMR: δ 7.49-7.16 (m, 15H, CH, arom), 5.32 (ddd, 1H, H-2, $J_{1a,2}$ 5.6 Hz, $J_{1b,2}$ 8.3 Hz, $J_{2,3}$ 6.4 Hz), 4.81 (ddd, 1H, H-5, $J_{4,5}$ 3.1 Hz, $J_{5,6a}$ $J_{5,6b}$ 6.1 Hz), 4.77 (dd, 1H, H-6a, $J_{6a,6b}$ -9.1 Hz), 4.64 (AB, 2H, CH_2, Bn, J -12.4 Hz), 4.45 (AB, 2H, CH_2, Bn, J -11.6 Hz), 4.30 (dd, 1H, H-6b), 4.00 (t, 1H, H-4, $J_{3,4}$ 4.2 Hz), 3.40 (dd, 1H, H-3), 1.76 (s, 3H, CH_3, Ac), 1.14 (dd, 1H, H-1a, $J_{1a,1b}$ -14.6 Hz), 1.11 (dd, 1H, H-1b), 0.31, 0.25 (2x s, 6H, $SiCH_3$). $^{13}C\{^1H\}$ NMR: δ 169.7 (C=O), 137.9, 136.8, 136.5 (Cq, arom), 133.4, 129.1-127.7 (CH, arom), 83.0, 80.4, 76.0 (C-3, C-4, C-5), 74.7, 74.2 (CH_2, Bn), 70.5 (C-2), 69.2 (C-6), 20.8 (CH_3, Ac), 17.7 (C-1), -2.8, -3.0 ($SiCH_3$).

2-*O*-Acetyl-3,6-anhydro-4-*O*-benzyl-1-deoxy-1-dimethylphenylsilyl-D-glucitol (6) - Cyclic sulfate **5** (0.31 g, 0.52 mmol) was dissolved in 90% aqueous THF (5 mL) and $NaHCO_3$ (88 mg, 1.04 mmol) was added. The mixture was heated to reflux for 2 h, cooled to 50°C, and H_2SO_4 (2 drops) was added. After stirring at 50°C for 1 h, the mixture was cooled to rt, a saturated solution of $NaHCO_3$ was added and the mixture extracted with Et_2O (2x 10 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated before purification on silica gel to afford **6** as a colorless oil. Yield 0.19 g (87%). R_f 0.2 (Et_2O/light petroleum, 1/1, v/v). $[\alpha]_D^{20}$ +1.1 (c 1). ^1H NMR: δ 7.45-7.25 (m, 10H, H-arom), 5.34 (dt, 1H, H-2, $J_{1a,2}$ $J_{2,3}$ 5.8 Hz, $J_{1b,2}$ 8.3 Hz), 4.56 (AB, 2H, CH_2, Bn, J -11.6 Hz), 4.23 (m, 1H, H-5), 4.02 (dd, 1H, H-4, $J_{3,4}$ 7.0 Hz, $J_{4,5}$ 5.4 Hz), 3.84 (dd, 1H, H-6a, $J_{5,6a}$ 2.6 Hz, $J_{6a,6b}$ -9.8 Hz), 3.72 (dd, 1H, H-3), 3.65 (dd, 1H, H-6b, $J_{5,6b}$ 4.3 Hz), 3.01 (d, 1H, OH, J 9.4 Hz), 1.80 (s, 3H, CH_3, Ac), 1.25 (dd, 1H, H-1a, $J_{1a,1b}$ -14.6 Hz), 1.17 (dd, 1H, H-1b), 0.30, 0.26 (2x s, 6H, $SiCH_3$). $^{13}C\{^1H\}$ NMR: δ 170.1 (C=O), 138.4, 137.1 (Cq, arom), 133.4, 128.8-127.6 (CH, arom), 81.4, 78.9 (C-3, C-4), 73.2, 72.6 (CH_2, Bn, C-6), 70.7, 70.0 (C-2, C-5), 20.8 (CH_3, Ac), 18.9 (C-1), -2.3, -2.9 ($SiCH_3$).

1,4-Anhydro-L-gulitol (7) - A solution of NaOAc (0.5 g) in AcOH (5 mL) was added to **6** (0.19 g, 0.45 mmol), followed by KBr (72 mg, 0.54 mmol). The mixture was cooled (10°C) and AcOOH (2.5 mL, 30% in AcOH) was added dropwise in the dark. After 2 h, the mixture was diluted with EtOAc (30 mL) and poured into a cooled (0°C) solution of $Na_2S_2O_3$ (5 mL, 15%). The layers were separated and to the organic phase was added aqueous $NaHCO_3$ (10 mL, 15%), followed by solid $NaHCO_3$ until no more gas evolved. The organic phase was washed with H_2O (10 mL), dried ($MgSO_4$) and solvents were evaporated *in vacuo*. The residue was coevaporated with toluene (2x 5 mL) and purified on silica gel to give 2-*O*-acetyl-3,6-anhydro-4-*O*-benzyl-D-glucitol. Yield 85 mg (64%). R_f 0.5 (EtOAc/MeOH, 19/1, v/v). $[\alpha]_D^{20}$ +11.1 (c 1). ^1H NMR: δ 7.41-7.25 (m, 5H,

H-arom), 5.16 (q, 1H, H-2, $J_{1a,2}$ $J_{2,3}$ 5.5 Hz, $J_{1b,2}$ 8.1 Hz), 4.62 (AB, 2H, CH_2, Bn, J -11.4 Hz), 4.29 (m, 1H, H-5), 4.22-4.18 (m, 2H, H-3, H-4), 3.96 (dd, 1H, H-6a, $J_{5,6a}$ 1.7 Hz, $J_{6a,6b}$ -10.1 Hz), 3.85 (m, 1H, H-1), 3.73 (dd, 1H, H-6b, $J_{5,6b}$ 3.6 Hz), 3.04 (d, 1H, OH, J 8.4 Hz), 2.20 (bs, 1H, OH), 2.06 (s, 3H, CH_3, Ac). $^{13}C\{^1H\}$ NMR: δ 170.6 (C=O), 136.9 (Cq, arom), 128.5, 128.1, 127.7 (CH, arom), 79.9, 77.1 (C-3, C-4), 73.2 (CH_2, Bn, C-6), 72.6, 70.0 (C-2, C-5), 62.4 (C-1), 21.0 (CH_3, Ac). The resulting alcohol (85 mg, 0.29 mmol) was dissolved in MeOH (3 mL) and KO*t*-Bu was added (6 mg, 0.05 mmol). The mixture was stirred for 8 h, neutralized with Dowex-H^+, filtered and concentrated. The residue was applied onto a column of silica gel and elution effected with EtOAc/MeOH (99/1, v/v) to give 3,6-anhydro-4-*O*-benzyl-D-glucitol as an oil. Yield 67 mg (91%). R_f 0.4 (EtOAc/MeOH, 19/1, v/v). $[\alpha]_D^{20}$ -21.3 (c 0.5). ^1H NMR: δ 7.40-7.26 (m, 5H, H-arom), 4.68 (AB, 2H, CH_2, Bn, J -11.6 Hz), 4.29-3.73 (m, 8H, H-1, H-2, H-3, H-4, H-5, H-6). $^{13}C\{^1H\}$ NMR: δ 137.2 (Cq, arom), 128.5, 128.0, 127.7 (CH, arom), 79.0, 78.2 (C-3, C-4), 73.9, 72.4 (CH_2, Bn, C-6), 69.0 (C-2, C-5), 64.4 (C-1). The deacetylated product (67 mg, 0.26 mmol) was dissolved in MeOH (2 mL) and degassed before the addition of 10% Pd-C (20 mg). A H_2-atmosphere was introduced and the mixture stirred until TLC-analysis showed the absence of UV-positive products. The catalyst was removed by filtration over Hyflo followed by rinsing with MeOH. Concentration afforded **7**, pure enough for spectral analysis. Yield 43 mg (100%). $[\alpha]_D^{20}$ +8.7 (c 1, H_2O). Mp 107°C. ^1H NMR (COSY): δ 4.41 (dt, 1H, H-2, $J_{2,3}$ 4.8 Hz, $J_{1a,2}$ $J_{1b,2}$ 6.6 Hz), 4.27 (t, 1H, H-3, $J_{3,4}$ 4.2 Hz), 3.96 (dd, 1H, H-1a, $J_{1a,1b}$ -9.0 Hz), 3.92 (dt, 1H, H-5, $J_{5,6a}$ 3.4 Hz, $J_{5,6b}$ $J_{4,5}$ 6.3 Hz), 3.89 (dd, 1H, H-4), 3.72 (dd, 1H, H-6a, $J_{6a,6b}$ -11.7 Hz), 3.70 (dd, 1H, H-1b), 3.60 (dd, 1H, H-6b). $^{13}C\{^1H\}$ NMR: δ 80.8 (C-4), 71.9, 71.6, 71.1 (C-2, C-3, C-5), 70.8 (C-1), 63.2 (C-6).

2,5-Anhydro-3,4-di-*O*-benzyl-1-deoxy-1-dimethylphenylsilyl-L-iditol (8) + 2,6-anhydro-3,4-di-*O*-benzyl-1-deoxy-1-dimethylphenylsilyl-D-glucitol (9) - To a solution of cyclic sulfate **5** (0.17 g, 0.29 mmol) in a mixture of dry THF (1 mL) and MeOH (2 mL) was added a freshly prepared solution of LiOMe in MeOH (0.35 mL, 1 M). After 3 h, TLC analysis indicated the complete conversion of **5** into baseline material. Concentrated H_2SO_4 (2 drops) was added and stirring continued at 50°C for 3 h. Work-up was executed as described in the preparation of **6** to give **8** and **9** as a mixture of isomers (ratio 5:2) after silica gel column chromatography (elution: Et_2O/light petroleum, 1/1, v/v). Yield 0.11 g (86%). R_f 0.7 (Et_2O/light petroleum, 3/1, v/v). Compound **8**: ^1H NMR: δ 7.54-7.20 (m, 15H, H-arom), 4.43 (AB, 2H, CH_2, Bn, J -11.8 Hz), 4.31 (AB, 2H, CH_2, Bn, J -11.6 Hz), 4.22 (ddd, 1H, H-2, $J_{1a,2}$ 7.6 Hz, $J_{1b,2}$ 7.3 Hz, $J_{2,3}$ 3.5 Hz), 4.13 (q, 1H, H-5), 4.04 (dd, 1H, H-4, $J_{3,4}$ 1.5 Hz, $J_{4,5}$ 5.3 Hz), 3.77 (dd, 1H, H-6a, $J_{5,6a}$ 5.5 Hz, $J_{6a,6b}$ -11.6 Hz), 3.67 (dd, 1H, H-6b, $J_{5,6b}$ 4.9 Hz), 3.60 (dd, 1H, H-3), 1.32 (dd, 1H, H-1a, $J_{1a,1b}$ -14.3 Hz), 1.19 (dd, 1H, H-1b), 0.33, 0.31 (2x s, 6H, $SiCH_3$). $^{13}C\{^1H\}$ NMR: δ 138.9, 137.8, 137.4 (Cq, arom), 133.5, 128.7-127.3 (CH, arom), 82.9, 82.7 (C-3, C-4), 78.5, 77.5 (C-2, C-5), 72.2, 71.5 (CH_2, Bn), 61.6 (C-6), 15.7 (C-1), -2.2, -2.7 ($SiCH_3$). Compound **9**: ^1H NMR: δ 7.53-7.18 (m, 15H, H-arom), 4.43 (s, 2H, CH_2, Bn), 4.40 (AB, 2H, CH_2, Bn, J -11.8 Hz), 4.00-3.94 (m, 1H, H-5), 3.76-3.68 (m, 3H, H-2, H-3, H-4), 3.35-3.21 (m, 2H, H-6), 2.04 (d, 1H, OH, J 8.6 Hz), 1.29 (dd, 1H, H-1a, $J_{1a,1b}$ -14.8 Hz, $J_{1a,2}$ 9.2), 0.87 (dd, 1H, H-1b, $J_{1b,2}$ 5.4 Hz), 0.31, 0.29 (2x s, 6H, $SiCH_3$). $^{13}C\{^1H\}$ NMR: δ 137.9, 137.7 (Cq, arom), 133.6, 128.9-127.7 (CH, arom), 76.4, 75.6 (C-3, C-4), 73.2, 72.7 (CH_2, Bn), 72.2 (C-2), 66.9 (C-6), 64.5 (C-5), 17.4 (C-1), -1.8, -2.8 ($SiCH_3$).

2,5-Anhydro-3,4-di-*O*-benzyl-L-iditol (11) + 1,5-anhydro-2,3-di-*O*-benzyl-L-gulitol (12) - Treatment of the mixture of **8** and **9** (0.48 g, 1.05 mmol) with KBr and AcO_2H was executed as described for oxidative unmasking of **6**. The crude product was applied onto a silica gel column and elution effected with Et_2O to give **12**. Yield 75 mg (21%). R_f 0.3 (Et_2O). $[\alpha]_D^{20}$ +19.9 (c 1). ^1H NMR: δ 7.37-7.25 (m, 10H, H-arom), 4.56 (s, 2H, CH_2, Bn), 4.50 (AB, 2H, CH_2, Bn, J -12.2 Hz),

4.05-3.95 (m, 1H, H-2), 3.91-3.36 (m, 7H, H-1, H-3, H-4, H-5, H-6), 2.10 (bs, 1H, OH), 1.73 (bs, 1H, OH). $^{13}C\{^1H\}$ NMR: δ 137.4, 137.2 (Cq, arom), 128.6-127.8 (CH, arom), 74.7, 73.4 (C-3, C-4, C-5), 72.9, 72.6 (CH_2, Bn), 66.7 (C-1), 64.6 (C-2), 62.3 (C-6). Further elution (Et_2O/MeOH, 49/1, v/v) afforded **11**. Yield 0.18 g (50%). R_f 0.2 (Et_2O). $[\alpha]_D^{20}$ +38.8 (c 1). ^1H NMR: δ 7.38-7.26 (m, 10H, H-arom), 4.54 (AB, 4H, CH_2, Bn, *J* -12.0 Hz), 4.26 (q, 2H, H-2, H-5, *J* 4.5 Hz), 4.14 (bd, 2H, H-3, H-4), 3.86-3.83 (m, 4H, H-1, H-6), 2.33 (s, 1H, OH). $^{13}C\{^1H\}$ NMR: δ 137.3 (Cq, arom), 128.4, 127.9, 127.5 (CH, arom), 82.3, 79.9 (C-2, C-3, C-4, C-5), 72.1 (CH_2, Bn), 61.4 (C-1, C-6).

2,5-Anhydro-L-iditol (13) - Compound **11** (0.18 g, 0.52 mmol) was hydrogenated as described for the synthesis of **7** to give crude **13** as an oil. Yield 82 mg (96%). Crystallization from EtOH afforded white crystals (50 mg). See Chapter I.

2-*O*-Acetyl-3,4-di-*O*-benzyl-1-deoxy-1-dimethylphenylsilyl-5,6-di-*O*-isopropylidene-D-altritol (15a) - Compound **14a**[13] (2.40 g, 4.60 mmol) was acetylated as described in the synthesis of **3** to give **15a** as an oil after purification by silica gel. Yield 2.14 g (83%). R_f 0.8 (Et_2O/light petroleum, 1/1, v/v). $[\alpha]_D^{20}$ +16.3 (c 0.5). ^1H NMR: δ 7.49-7.25 (m, 15H, H-arom), 5.34 (m, 1H, H-2), 4.66 (s, CH_2, Bn), 4.53 (AB, 2H, CH_2, Bn, *J* -11.8 Hz), 4.27 (dt, 1H, H-5, $J_{4,5}$ 5.4 Hz, $J_{5,6a}$ $J_{5,6b}$ 6.4 Hz), 3.91 (m, 2H, H-6), 3.79 (dd, 1H, H-4, $J_{3,4}$ 3.2 Hz), 3.39 (dd, 1H, H-3, $J_{2,3}$ 5.4 Hz), 1.65 (s, 3H, CH_3, Ac), 1.39, 1.32 (2x s, 6H, CH_3, isoprop), 1.19 (m, 2H, H-1), 0.30, 0.27 (2x s, 6H, $SiCH_3$). $^{13}C\{^1H\}$ NMR: δ 169.6 (C=O), 138.1, 138.0, 137.7 (Cq, arom), 133.2, 128.4-127.3 (CH, arom), 108.1 (Cq, isoprop), 81.4, 78.9, 75.2 (C-3, C-4, C-5), 73.4, 73.2 (CH_2, Bn), 70.0 (C-2), 65.8 (C-6), 26.2, 24.8 (CH_3, isoprop), 20.6 (CH_3, Ac), 18.5 (C-1), -2.8, -3.1 ($SiCH_3$).

2-*O*-Acetyl-3,4-di-*O*-benzyl-1-deoxy-1-dimethylphenylsilyl-D-altritol (16a) - Compound **15a** (2.14 g, 3.81 mmol) was deacetonated as described in the synthesis of **3** to give **16a** as an oil after silica gel column chromatography. Yield 1.64 g (83%). R_f 0.5 (Et_2O). ^1H NMR: δ 7.50-7.24 (m, 15H, CH, arom), 5.37 (m, 1H, H-2), 4.60 (AB, 2H, CH_2, Bn, *J* -11.6 Hz), 4.56 (s, 2H, CH_2, Bn), 3.92-3.58 (m, 5H, H-3, H-4, H-5, H-6), 3.17 (bs, 1H, OH), 2.18 (bs, 1H, OH), 1.70 (s, 3H, CH_3, Ac), 1.17 (dd, 1H, H-1a, $J_{1a,1b}$ -11.2 Hz, $J_{1a,2}$ 5.2 Hz), 0.85 (dd, 1H, H-1b, $J_{1b,2}$ 4.7 Hz), 0.31, 0.28 (2x s, 6H, $SiCH_3$). $^{13}C\{^1H\}$ NMR: δ 170.3 (C=O), 138.1, 137.8, 137.7 (Cq, arom), 133.2, 128.5-127.3 (CH, arom), 82.2, 79.0 (C-3, C-4), 73.5, 72.8 (CH_2, Bn), 71.2, 70.5 (C-2, C-5), 63.4 (C-6), 20.6 (CH_3, Ac), 18.5 (C-1), -2.7, -3.2 ($SiCH_3$).

2-*O*-Acetyl-3,4-di-*O*-benzyl-5,6-*O*-(cyclic sulfate)-1-deoxy-1-dimethylphenylsilyl-D-altritol (17a) - Diol **16a** (0.58 g, 1.03 mmol) was treated with thionylchloride and subsequently oxidized with $RuCl_3$ as described in the preparation of **5** to give **17a** as an oil after silica gel column chromatography. Yield 0.48 g (79%). R_f 0.6 (Et_2O/light petroleum, 1/1, v/v). $[\alpha]_D^{20}$ +28.8 (c 2). ^1H NMR: δ 7.48-7.18 (m, 15H, CH, arom), 5.17-5.07 (m, 2H, H-2, H-5), 4.63 (m, 1H, H-6a), 4.48 (AB, 2H, CH_2, Bn, *J* -11.1 Hz), 4.33 (d, 2H, CH_2, Bn, *J* -2.0), 4.33 (dd, 1H, H-6b, $J_{5,6b}$ 6.7 Hz, $J_{6a,6b}$ -8.8 Hz), 3.97 (m, 1H, H-4), 3.52 (dd, 1H, H-3, $J_{2,3}$ 5.6 Hz, $J_{3,4}$ 3.4 Hz), 1.70 (s, 3H, CH_3, Ac), 1.08-0.96 (m, 2H, H-1), 0.32, 0.29 (2x s, 6H, $SiCH_3$). $^{13}C\{^1H\}$ NMR: δ 169.9 (C=O), 137.6, 136.7 (Cq, arom), 133.4, 128.8-127.7 (CH, arom), 82.1, 80.8, 76.4 (C-3, C-4, C-5), 74.3, 73.6 (CH_2, Bn), 69.5 (C-2), 69.3 (C-6), 20.6 (CH_3, Ac), 17.9 (C-1), -2.8, -3.0 ($SiCH_3$).

2,5-Anhydro-3,4-di-*O*-benzyl-1-deoxy-1-dimethylphenylsilyl-L-galactitol (18a) + 2,6-anhydro-3,4-di-*O*-benzyl-1-deoxy-1-dimethylphenylsilyl-D-altritol (19a) - Cyclic sulfate **17a** (0.30 g, 0.51 mmol) was treated with LiOMe, followed by H_2SO_4 as described for the cyclization of **5**. After purification, compounds **18a** and **19a** were obtained as a mixture of isomers (ratio 6:1). Yield 0.16

g (70%). R_f 0.4 (Et_2O/light petroleum, 3/1, v/v). Compound **18a**: $[\alpha]_D^{20}$ +15.4 (c 2). ^1H NMR: δ 7.54-7.25 (m, 15H, H-arom), 4.63 (AB, 2H, CH_2, Bn, J -11.6 Hz), 4.57 (AB, 2H, CH_2, Bn, J -12.1 Hz), 4.22 (dd, 1H, H-6a, $J_{5,6a}$ 4.0 Hz, $J_{6a,6b}$ -7.9 Hz), 4.06 (dd, 1H, H-6b, $J_{5,6b}$ 4.7 Hz), 3.96 (ddd, 1H, H-2, $J_{1a,2}$ 8.6 Hz, $J_{1b,2}$ 4.0 Hz, $J_{2,3}$ 6.2 Hz), 3.74-3.68 (m, 3H, H-3, H-4, H-5), 2.56 (t, 1H, OH, J 4.2 Hz), 1.43 (dd, 1H, H-1a, $J_{1a,1b}$ -14.5 Hz), 1.14 (dd, 1H, H-1b), 0.31 (s, 6H, $SiCH_3$). $^{13}C\{^1H\}$ NMR: δ 138.0, 137.6 (Cq, arom), 133.6, 128.5-127.3 (CH, arom), 80.9, 78.4, 77.4, 77.2 (C-2, C-3, C-4, C-5), 73.5, 72.9 (CH_2, Bn), 62.3 (C-6), 16.9 (C-1), -2.1, -2.3 ($SiCH_3$). Compound **19a**: $^{13}C\{^1H\}$ NMR: δ 138.2, 137.6 (Cq, arom), 133.4, 128.4-127.3 (CH, arom), 77.5, 76.1 (C-3, C-4), 73.1, 72.8 (CH_2, Bn), 70.1 (C-2), 67.2 (C-6), 63.5 (C-5), 17.8 (C-1), -2.3, -2.9 ($SiCH_3$).

2,5-Anhydro-3,4-di-*O*-benzyl-L-galactitol (20a) + 1,5-anhydro-2,3-di-*O*-benzyl-L-talitol (21a) - Treatment of the isomeric mixture of silanes **18a** and **19a** (0.16 g, 0.35 mmol) with KBr and AcO_2H was executed as described for the oxidative unmasking of **6**. The oil obtained after work-up was applied onto a column of silica gel and elution effected with EtOAc to give **21a**. Yield 13 mg (11%). R_f 0.2 (EtOAc). $^{13}C\{^1H\}$ NMR: δ 137.4, 137.2 (Cq, arom), 128.6-127.8 (CH, arom), 74.7, 73.4 (C-2, C-3, C-4), 72.9, 72.6 (CH_2, Bn), 66.7 (C-6), 64.6 (C-5), 62.3 (C-1). Further elution gave **20a**. Yield 77 mg (64%). R_f 0.1 (EtOAc). $[\alpha]_D^{20}$ 0 (c 1). ^1H NMR: δ 7.35-7.26 (m, 10H, H-arom), 4.67 (AB, 4H, CH_2, Bn, J -11.8 Hz), 4.21-4.10 (m, 4H, H-2, H-3, H-4, H-5), 3.88 (dd, 2H, H-1a, H-6a, $J_{1a,1b}$ $J_{6a,6b}$ -11.7 Hz, $J_{1a,2}$ $J_{5,6a}$ 5.0 Hz), 3.78 (dd, 2H, H-1b, H-6b, $J_{1b,2}$ $J_{5,6b}$ 4.5 Hz), 2.70 (bs, 1H, OH). $^{13}C\{^1H\}$ NMR: δ 138.0 (Cq, arom), 128.6, 128.1, 127.6 (CH, arom), 78.8 (C-2, C-3, C-4, C-5), 73.6 (CH_2, Bn), 61.9 (C-1, C-6).

2,5-Anhydro-galactitol (22a) - Compound **20a** (77 mg, 0.22 mmol) was hydrogenated as described for the synthesis of **7** to give **22a** as a syrup. Yield 32 mg (87%). R_f 0.4 (MeOH). $[\alpha]_D^{20}$ 0 (c 0.3, H_2O). ^1H NMR: see Table 3, Chapter I. $^{13}C\{^1H\}$ NMR (MeOD): δ 80.2 (C-2, C-5), 71.8 (C-3, C-4), 60.8 (C-1, C-6).

3,4-di-*O*-benzyl-1-deoxy-1-dimethylphenylsilyl-5,6-di-*O*-isopropylidene-D-iditol (14b) - A solution of 3,4-di-*O*-benzyl-1-deoxy-1-dimethylphenylsilyl-D-iditol (Chapter I) was dissolved in acetone (3 mL) and 2,2-dimethoxypropane (0.44 mL, 3.55 mmol) and *p*-TsOH (18 mg, 0.07 mmol) were added. After stirring for 1.5 h, a saturated solution of $NaHCO_3$ (4 mL) was added, and 1,4-dioxane was removed *in vacuo*. Et_2O (20 mL) was added, the layers were separated and the organic layer was washed with brine (15 mL), dried ($MgSO_4$) and concentrated. The residue was purified on silica gel (elution: Et_2O/light petroleum, 1/2, v/v) to give **14b** as an oil. Yield 0.28 g (76%). R_f 0.8 (Et_2O/light petroleum, 3/1, v/v). $[\alpha]_D^{20}$ 15.2 (c 2.0). ^1H NMR: δ 7.53-7.21 (m, 15H, H-arom), 4.64 (s, 2H, CH_2, Bn), 4.51 (AB, 2H, CH_2, Bn, J -11.3 Hz), 4.33 (ddd, 1H, H-5, $J_{4,5}$ 5.5 Hz, $J_{5,6a}$ 6.4 Hz, $J_{5,6b}$ 7.5 Hz), 3.96 (m, 1H, H-2), 3.86 (dd, 1H, H-6a, $J_{6a,6b}$ -8.1 Hz), 3.71 (dd, 1H, H-6b), 3.50 (t, 1H, H-4, $J_{3,4}$ 5.2 Hz), 3.31 (dd, 1H, H-3, $J_{2,3}$ 3.1 Hz), 2.33 (d, 1H, OH, J 7.5 Hz), 1.41, 1.33 (2x s, 6H, CH_3, isoprop), 1.10 (dd, 1H, H-1a, $J_{1a,1b}$ -14.7 Hz, $J_{1a,2}$ 9.1 Hz), 1.00 (dd, 1H, H-1b, $J_{1b,2}$ 4.9 Hz), 0.32 (s, 6H, $SiCH_3$). $^{13}C\{^1H\}$ NMR: δ 139.3, 138.2, 137.9 (Cq, arom), 133.5, 128.7-127.5 (CH, arom), 108.7 (Cq, arom), 83.2, 78.2, 76.2 (C-3, C-4, C-5), 74.1, 73.7 (CH_2, Bn), 68.1 (C-2), 65.8 (C-6), 26.4, 25.5 (CH_3, isoprop), 22.2 (C-1), -2.0, -2.7 ($SiCH_3$).

2-*O*-Acetyl-3,4-di-*O*-benzyl-1-deoxy-1-dimethylphenylsilyl-5,6-di-*O*-isopropylidene-D-iditol (15b) - Compound **14b** (0.28 g, 0.54 mmol) was acetylated and purified as in the synthesis of **3** to give **15b** as an oil. Yield 0.29 g (96%). R_f 0.4 (Et_2O/light petroleum, 1/1, v/v). ^1H NMR: δ 7.48-7.14 (m, 15H, H-arom), 5.34 (dt, 1H, H-2, $J_{1a,2}$ $J_{2,3}$ 5.8 Hz, $J_{1b,2}$ 8.3 Hz), 4.67 (AB, CH_2, Bn, J -11.3 Hz), 4.48 (AB, 2H, CH_2, Bn, J -11.6 Hz), 4.21 (m, 1H, H-5), 3.81 (dd, 1H, H-6a, $J_{5,6a}$ 6.3 Hz,

$J_{6a,6b}$ -8.0 Hz), 3.66 (t, 1H, H-6b, $J_{5,6b}$ 7.9 Hz), 3.53-3.40 (m, 2H, H-3, H-4), 1.77 (s, 3H, CH_3, Ac), 1.40, 1.33 (2x s, 6H, CH_3, isoprop), 1.26 (dd, 1H, H-1a, $J_{1a,1b}$ -14.6 Hz), 1.11 (dd, 1H, H-1b), 0.29, 0.25 (2x s, 6H, $SiCH_3$). $^{13}C\{^1H\}$ NMR: δ 170.1 (C=O), 138.6, 138.1 (Cq, arom), 133.6, 129.1-127.7 (CH, arom), 109.1 (Cq, isoprop), 81.0, 78.3, 76.4 (C-3, C-4, C-5), 73.9, 73.8 (CH_2, Bn), 71.0 (C-2), 65.8 (C-6), 26.5, 25.8 (CH_3, isoprop), 21.1 (CH_3, Ac), 18.3 (C-1), -2.4, -2.7 ($SiCH_3$).

2-*O*-Acetyl-3,4-di-*O*-benzyl-1-deoxy-1-dimethylphenylsilyl-D-iditol (16b) - Deacetonation of compound **15b** (0.29 g, 0.52 mmol) as described in the synthesis of **3** gave **16b** after purification. Yield 0.25 g (92%). R_f 0.2 (Et_2O/light petroleum, 3/1, v/v). $[\alpha]_D^{20}$ -4.7 (c 2.5). ^1H NMR: δ 7.48-7.22 (m, 15H, CH, arom), 5.27 (m, 1H, H-2), 4.66 (AB, 2H, CH_2, Bn, J -11.6 Hz), 4.57 (AB, 2H, CH_2, Bn, J -11.1), 3.76-3.64 (m, 2H, H-5, H-6a), 3.57-3.46 (m, 3H, H-3, H-4, H-6b), 1.82 (s, 3H, CH_3, Ac), 1.25-1.17 (m, 1H, H-1), 0.31, 0.28 (2x s, 6H, $SiCH_3$). $^{13}C\{^1H\}$ NMR: δ 170.5 (C=O), 138.2, 138.0, 137.7 (Cq, arom), 133.4, 128.9-127.5 (CH, arom), 80.7, 78.5 (C-3, C-4), 74.5, 74.3 (CH_2, Bn), 70.8, 70.5 (C-2, C-5), 63.9 (C-6), 20.9 (CH_3, Ac), 18.0 (C-1), -2.7, -2.9 ($SiCH_3$).

2-*O*-Acetyl-3,4-di-*O*-benzyl-5,6-*O*-(cyclic sulfate)-1-deoxy-1-dimethylphenylsilyl-D-iditol (17b) - Diol **16b** (0.25 g, 0.47 mmol) was converted into the corresponding cyclic sulfate as described in the preparation of **5** to give **17b** as an oil after silica gel column chromatography. Yield 0.20 g (74%). R_f 0.6 (Et_2O/light petroleum, 3/1, v/v). ^1H NMR: δ 7.48-7.20 (m, 15H, CH, arom), 5.32 (dt, 1H, H-2, $J_{1a,2}$ $J_{2,3}$ 5.8 Hz, $J_{1b,2}$ 8.3 Hz), 4.88 (m, 1H, H-5), 4.82 (dd, 1H, H-6a, $J_{5,6a}$ 6.8 Hz, $J_{6a,6b}$ -8.3 Hz), 4.63 (AB, 2H, CH_2, Bn, J -12.3 Hz), 4.50 (AB, 2H, CH_2, Bn, J -11.6), 4.35 (dd, 1H, H-6b, $J_{5,6b}$ 6.0 Hz), 3.82-3.70 (m, 2H, H-3, H-4), 1.76 (s, 3H, CH_3, Ac), 1.26 (dd, 1H, H-1a, $J_{1a,1b}$ -14.6 Hz), 1.11 (dd, 1H, H-1b), 0.30, 0.24 (2x s, 6H, $SiCH_3$). $^{13}C\{^1H\}$ NMR: δ 169.8 (C=O), 137.8, 136.9, 136.8 (Cq, arom), 133.4, 129.2-127.8 (CH, arom), 83.0, 79.5, 75.6 (C-3, C-4, C-5), 74.2, 73.8 (CH_2, Bn), 69.9 (C-2), 69.8 (C-6), 20.9 (CH_3, Ac), 18.2 (C-1), -2.8, -3.0 ($SiCH_3$).

2,5-Anhydro-3,4-di-*O*-benzyl-1-deoxy-1-dimethylphenylsilyl-L-glucitol (18b) + 2,6-anhydro-3,4-di-*O*-benzyl-1-deoxy-1-dimethylphenylsilyl-D-iditol (19b) - Cyclic sulfate **17b** (0.20 g, 0.34 mmol) was treated with LiOMe, followed by H_2SO_4 as described for **5**. Flash chromatography gave compounds **18b** and **19b** (ratio 4:1). Yield 0.10 g (66%). R_f 0.7 (toluene/acetone, 85/15, v/v). Compound **18b**: ^1H NMR: δ 7.55-7.25 (m, 15H, CH, arom), 4.47 (s, 2H, CH_2, Bn), 4.30 (AB, 2H, CH_2, Bn, J -12.1 Hz), 4.12), 4.12 (m, 1H, H-2), 3.92 (m, 2H, H-5, H-6a), 3.74 (dd, 1H, H-6b, $J_{5,6b}$ 1.8 Hz, $J_{6a,6b}$ -9.8 Hz), 3.63 (d, 1H, H-4, $J_{4,5}$ 3.7 Hz), 3.56 (d, 1H, H-3, $J_{2,3}$ 3.2 Hz), 1.38 (dd, 1H, H-1a, $J_{1a,1b}$ -14.2 Hz, $J_{1a,2}$ 7.3 Hz), 1.20 (dd, 1H, H-1b, $J_{1b,2}$ 7.5 Hz), 0.31 (s, 6H, $SiCH_3$). $^{13}C\{^1H\}$ NMR: δ 138.8, 137.6 (Cq, arom), 133.4, 128.6-127.9 (CH, arom), 83.6, 83.2, 79.0 (C-2, C-3, C-4, C-5), 71.7, 70.8 (CH_2, Bn), 63.0 (C-6), 15.2 (C-1), -2.3, -2.7 ($SiCH_3$).

2,5-Anhydro-3,4-di-*O*-benzyl-L-glucitol (20b) + 1,5-anhydro-2,3-di-*O*-benzyl-L-iditol (21b) - Treatment of the isomeric mixture of silanes **18b** and **19b** (0.10 g, 0.22 mmol) with KBr and AcO_2H was executed as described for the unmasking of **6**. The oil obtained after work-up was applied onto a column of silica gel (elution: Et_2O/light petroleum, 2/1, v/v) to give **21b**. Yield 10 mg (14%). R_f 0.4 (Et_2O). $^{13}C\{^1H\}$ NMR: δ 137.6, 137.0 (Cq, arom), 128.8-127.5 (CH, arom), 75.7, 74.1, 73.0 (C-2, C-3, C-4), 71.9, 71.8 (CH_2, Bn), 66.3 (C-6), 64.6 (C-5), 60.9 (C-1). Further elution (3/1, v/v) afforded **20b**. Yield 0.42 g (57%). R_f 0.3 (Et_2O). $[\alpha]_D^{20}$ +30.9 (c 1). ^1H NMR: δ 7.52-7.25 (m, 10H, CH, arom), 4.56 (s, 2H, CH_2, Bn), 4.53 (AB, 2H, CH_2, Bn, J -11.8 Hz), 4.18-3.83 (m, 6H, H-1a, H-2, H-4, H-5, H-6), 3.80 (d, 1H, H-3, $J_{2,3}$ 2.8 Hz), 3.66 (dd, 1H, H-1b, $J_{1a,1b}$ -12.0 Hz, $J_{1b,2}$ 4.3 Hz). $^{13}C\{^1H\}$ NMR: δ 137.4, 137.0 (Cq, arom), 128.2-127.3 (CH, arom), 83.5, 83.2, 82.6, 80.4 (C-2, C-3, C-4, C-5), 71.7, 71.5 (CH_2, Bn), 62,4, 61.5 (C-1, C-6).

2,5-Anhydro-L-glucitol (22b) - Compound **20b** (42 mg, 0.12 mmol) was hydrogenated as described for the synthesis of **7** to give **22b** as a syrup. Yield 19 mg (97%). See Chapter I.

References and notes

1. van Delft, F.L.; van der Marel, G.A.; van Boom, J.H., *manuscript in preparation.*
2. Lohray, B.B. *Synthesis* **1992**, 1035.
3. van der Klein, P.A.M., PhD Thesis, Leiden University, 1992.
4. (a) van der Klein, P.A.M.; Filemon, W.; Veeneman, G.H.; van der Marel, G.A.; van Boom, J.H. *J. Carbohydr. Chem.* **1992**, *11*, 837 (b) van der Klein, P.A.M.; Boons, G.J.P.H.; Veeneman, G.H.; van der Marel, G.A.; van Boom, J.H. *Tetrahedron Lett.* **1989**, *30*, 5477. (c) van der Klein, P.A.M.; Filemon, W.; Broxterman, H.J.G.; van der Marel, G.A.; van Boom, J.H. *Synth. Commun.* **1992**, *22*, 1763.
5. (a) Skead, B.M.; Fleet, G.W.J.; Saunders, J.; Lamont, R.B. *Tetrahedron Lett.* **1993**, *34*, 6115. (b) Kim, K.S.; Joo, Y.H.; Kim, I.W.; Lee, K.R.; Cho, D.Y.; Kim, M.; Cho, I.H. *Synth. Commun.* **1994**, *24*, 1157. (c) Ko, S.Y.; Malik, M.; Dickinson, A.F. *J. Org. Chem.* **1994**, *59*, 2570. (d) Beauchamp, T.J.; Powers, J.P.; Rychnovski, S.D. *J. Am. Chem. Soc.* **1995**, *117*, 12873.
6. (a) van Delft, F.L.; van der Marel, G.A.; van Boom, J.H. *Tetrahedron Lett.* **1994**, *35*, 1091. (b) van Delft, F.L.; van der Marel, G.A.; van Boom, J.H. *Recl. Trav. Chim. Pays-Bas* **1994**, *113*, 339.
7. (a) Gray, G.R.; Hartman, F.C.; Barker, R. *J. Org. Chem.* **1965**, *30*, 2020. (a) Dehmlow, H.; Mulzer, J.; Seilz, C.; Strecker, A.R.; Kohlmann, A. *Tetrahedron Lett.* **1992**, *33*, 3607. (b) Martin, O.R.; Yang, F.; Xie, F. *ibid.* **1995**, *36*, 47.
8. Santoyo-González, F.; Calvo-Flores, F.G.; Hernández-Mateo, F.; Isac-Garcia, J.; García-Mendoza, P. *Abstracts of the VIIIth European Carbohydrate Symposium*, Sevilla, Spain, July 2-7, **1995**, A-81.
9. (a) Barker, R. *J. Org. Chem.* **1964**, *29*, 869. (b) Bock, K.; Pedersen, C.; Thøgersen, H. *Acta Chem. Scand.* **1981**, *B 35*, 441.
10. Compound **5** and **17b** did not dissolve in pure MeOH.
11. (a) Rao, V.S.; Perlin, A.S. *Can. J. Chem.* **1984**, *62*, 886. (b) Rafka, R.J.; Morton, B.J. *Carbohydr. Res.* **1994**, *260*, 155.
12. Hydrogenation of **12** gave 1,5-anhydro-L-gulitol. Ness, R.K.; Fletcher Jr., H.G. *J. Am. Chem. Soc.* **1953**, *75*, 2619. See also reference 14.
13. Hydrogenation of **21a** and **21b** gave 1,5-anhydro-D-talitol and 1,5-anhydro-D-iditol, respectively. Rosenfeld, D.A.; Richtmyer, N.K.; Hudson, C.S. *J. Am. Chem. Soc.* **1948**, *70*, 2201. See also reference 14.
14. Bock, K.; Pedersen, C. *Adv. Carbohydr. Chem.* **1983**, *41*, 27.
15. (a) Que Jr., L.; Gray, G.R. *Biochemistry* **1974**, *13*, 146. (b) Koerner, T.A.W.; Voll, R.J.; Younathan, E.S. *Carbohydr. Res.* **1977**, *59*, 403.
16. Harmange, J.-C.; Figadère, B. *Tetrahedron: Asymmetry* **1993**, *4*, 1711.
17. Postema, M.H.D. *Tetrahedron* **1992**, *48*, 8545.

III

Stereocontrolled Hydroxymethylation of Carbohydrate Imines: Formal Synthesis of Destomic acid and Lincosamine[1]

Abstract

Nucleophilic addition of organometallic reagents to 6-tosylimino and 6-benzylimino derivatives of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose is investigated. Addition of several organometallics to benzylimine 7 mediated by $Ce(III)Cl_3$ or $CuI/BF_3{\cdot}Et_2O$ proceeds with high *syn*- or *anti*-diastereoselectivity, respectively. The resulting secondary amines are further processed to known precursors of destomic acid and lincosamine.

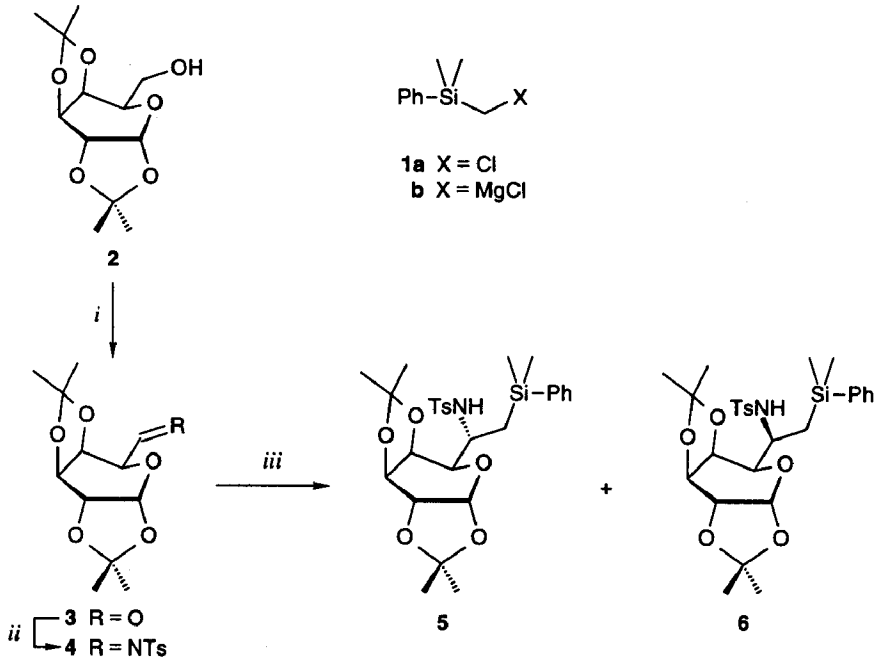
Introduction

Earlier studies from our[2] and other[3] laboratories revealed that Grignard derivative **1b** (Scheme 1), derived from commercially available (chloromethyl)dimethylphenylsilane (**1a**), is an effective reagent for the hydroxymethylation of carbonyl or hemiacetal functions in carbohydrates. In general, nucleophilic addition of **1b** proceeds[2a-d] with high diastereoselectivity resulting in the formation of the *syn*-hydroxysilane adduct. On the other hand, condensation of **1b** with the α-D-galacto-hexodialdo-1,5-pyranoside derivative **3** led predominantly[2e] to the *anti*-adduct, further elaboration of which gave the earlier prepared[4a] 6,7-*epimino* precursor of destomic acid. It occurred to us that the latter amino sugar may be prepared in a more straightforward manner by addition of **1b** to a corresponding imino derivative of **3**, followed by oxidative demasking of the silyl moiety. However, nucleophilic addition to imines is often accompanied by competing reactions as α-deprotonation and reductive dimerization, due to the relatively low electrophilicity of imine carbons. For this reason, the choice of reagents is restricted to relatively non-basic

nucleophiles (*e.g.* allylmetals[5a,b], enolates[5c] and cyanides[5d]) or imines lacking α-hydrogens[6]. Application of organometalloids of low basicity[7] or *in situ* activation of imines with a Lewis acid[8] also suppressed the occurence of side-reactions. Alternatively, more electrophilic imine analogues, including hydrazones[9], oximes[10] and nitrones[11] have been employed to give, after reduction of the resulting hydrazines (from hydrazones) or hydroxylamines (from oximes and nitrones), the secondary amines. Addition of organometallics to tosylimines[12], silylimines[13], phosphinylimines[14], sulfenylimines[15] and iminium ions[16] is also feasible. Moreover, recent studies involving mixed benzotriazole aminals[17] show great promise.

In this Chapter it is shown that chain-extension of the 6-benzylimino derivative of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**7**) under the influence of $CeCl_3$ proceeds stereoselectively to *syn*-condensation adducts, in the preparation of a precursor of destomic acid. In contrast, nucleophilic addition in the presence of $CuI/BF_3{\cdot}Et_2O$ shows opposite diastereofacial selectivity, leading to a useful precursor of lincosamine.

Scheme 1



Reagents and conditions

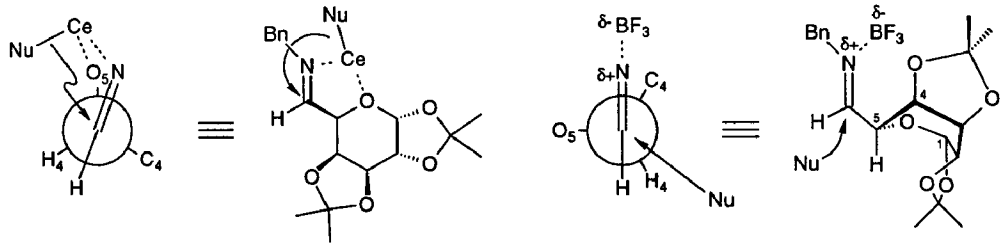
(*i*) DMSO, $(COCl)_2$, CH_2Cl_2, -60°C, 1 h then Et_3N, -60° → 0°C; (*ii*) *p*-TsN=S=O, CH_2Cl_2, 16 h; (*iii*) **1b**, CH_2Cl_2, THF, 0°C (**5**:**6** = 4:1, 49% overall).

At first instance, attention was focussed on the condensation of Grignard reagent **1b** with the highly electrophilic *N*-tosyl imine derivative **4** (Scheme 1). As demonstrated by

Weinreb *et al.*[12b], tosylimines are accessible by condensation of aldehydes with *N*-sulfinyl sulfonamides. Thus, 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**2**) was oxidized by the Swern procedure to give aldehyde **3** as an oil. Subsequent treatment of crude **3** with *N*-sulfinyl *p*-toluenesulfonamide[18] in CH_2Cl_2 resulted in liberation of SO_2 and the formation of tosylimine **4**, presumably involving a [2+2]-addition. Unfortunately, ^{1}H NMR analysis of the crude reaction mixture showed an incomplete conversion. The use of an excess of reagent (2.5 equiv.) and prolonged reaction time (16 h) did not improve the latter result. Moreover, tosylimine **4** was found to be unstable, *i.e.* purification of the compound led to decomposition. Grignard reaction was executed by dropwise addition of **1b** (5 equiv. in THF) to a solution of crude **4** (0°C) to give a more lipophilic product. Work-up and purification afforded the diastereomeric compounds *anti*-**5** and *syn*-**6** (49% yield) as an intractable mixture (ratio 4:1). The C-6 configuration of **5** and **6** was established after their respective conversion into amino alcohols **11** and **16** (Scheme 2) *via* oxidative demasking and Birch reduction. Unfortunately, lowering the reaction temperature or addition of an ethereal solution of **1b** not improve the stereoselective outcome of the condensation reaction. The same disappointing result was obtained by the application of a work-up procedure for the imine **4** comprising intermediate concentration under reduced pressure to a small volume followed by filtration of solids and addition of THF or ether. The inherent instability of the imine **4** urged us to abandone the preparation of aminosugars *via* nucleophilic addition to tosylimines.

An alternative approach for nucleophilic addition to alkylimines comprises the use of organocerium reagents which are superior, in terms of yield and stereoselectivity, over the traditional organolithium and magnesium reagents[7b,d-g]. The high promise of this methodology stimulated us to investigate the stereochemical outcome of the cerium-mediated addition of hydroxymethylating reagent **1b** to galactose imine **7** (Scheme 2). To this end isomerically pure[19] imine **7**, readily accessible by the reaction of benzylamine with aldehyde **3**, was treated with excess Grignard reagent **1b**, precomplexed with cerium(III)chloride[20] at low temperature. ^{1}H NMR analysis of the crude product revealed the presence of one diastereomer, obtained in 68% yield after silica gel column chromatography. The newly introduced C-6 stereocenter of the resulting *syn*-adduct **8** was unambiguously established to have the *R*-configuration by conversion into the reported[4] precursor **12** of destomic acid. Thus, benzyloxycarbonylation of **8** followed by oxidative unmasking (KBr, AcO_2H) of the silyl moiety[21,22] in the resulting urethane **9** gave alcohol **10** (71% yield). Hydrogenolysis of both *N*-protecting groups using Pearlman's catalyst gave the free amino derivative **11**. Subsequent treatment of **11** with benzyl chloroformate under Schotten-Bauman conditions afforded homogeneous **12** (64% yield based on **10**), which was in all aspects identical ($[\alpha]_D$, NMR) with an authentic sample[4]. The observed *syn*-stereoselectivity may be explained by complexation of the cerium(III) salts with the nitrogen and the α-oxygen atoms in **7**, *i.e.* Cram-chelation[23], thus directing the incoming nucleophile to the less sterically hindered *si* face of the imine[24] (Figure 1).

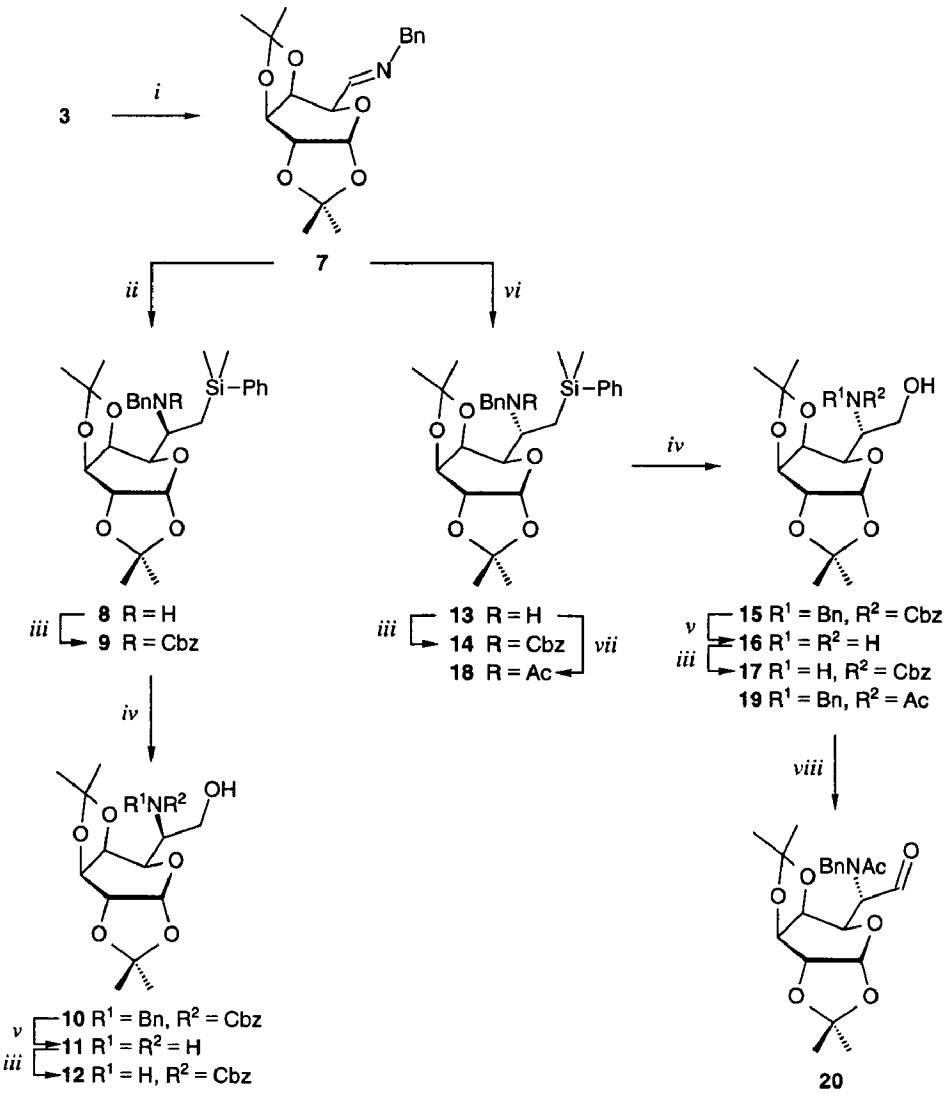
Figure 1. Nucleophilic addition to imine **7** following the Cram-chelation model (left) or the Felkin-Anh model (right).



In order to synthesize lincosamine, the sugar component of the antibiotic lincomycin[25], it was imperative that the nucleophilic addition of **1b** to the benzylimine derivative **7** would proceed with *anti*-stereofacial selectivity. Recently, it was shown[7b] that nucleophilic addition of organocopper(I) reagents to α-alkoxy imines in the presence of $BF_3{\cdot}Et_2O$[7a] gives the *anti*-adduct in high diastereomeric excess. Hence, precomplexation of Grignard reagent **1b** with CuI (diethyl ether, -40°C) and $BF_3{\cdot}Et_2O$ (-78°C), followed by the addition of imine **7** and slow warming to -40°C, gave *anti*-adduct **13** (70% yield) as a single diastereomer as revealed by proton NMR analysis. The *anti*-selectivity of the addition reaction was corroborated *via* transformation of **13** into known[4] compound **17** following the same four step procedure described above for the preparation of **12** from **8**. Moreover, **13** could be effectively converted into α-amino aldehyde **20**, a suitable precursor[26] of lincosamine, by the following three-step procedure. Thus, acetylation of **13** (→**18**) and oxidative unmasking of the silyl moiety in **18** (→**19**) gave, after Swern oxidation, aldehyde **20** (65% overall yield), the spectroscopic data of which were in full accord with those of the same compound prepared by Atsumi[26a] as well as Dondoni[26b]. The diastereoselectivity of the copper-mediated addition, leading to the *anti*-product **13**, may be rationalized with the Felkin-Anh model[27] (Figure 1). According to this model the preferred trajectory of the incoming nucleophile is determined by an orthogonal orientation of the ring oxygen and the imine function.

The excellent diastereofacial selectivity observed in the hydroxymethylation of imine **7** prompted us to investigate the chain-extension of **7** with other nucleophiles, *e.g.* vinylmagnesium bromide, thiazolyllithium[28] and furyllithium[29] (Scheme 3). The former two reagents represent synthetic equivalents of a formyl anion[30] while a furyl moiety can be transformed into a carboxylic acid by oxidation[31]. The results of the condensation reactions of **7** with the aforementioned nucleophiles, to give the respective adducts **21-26**, are collected in Table 1. In entry 3 and 4 it is shown that addition of vinylmagnesium bromide to **7**, under the influence of $CeCl_3$[32] or $CuI/BF_3{\cdot}Et_2O$, proceeds analogously as for **1b**, giving the respective *syn*- and *anti*-adducts **21** and **22** with excellent diastereoselectivity. On the other hand, the stereochemical outcome of the addition of

Scheme 2



Reagents and conditions

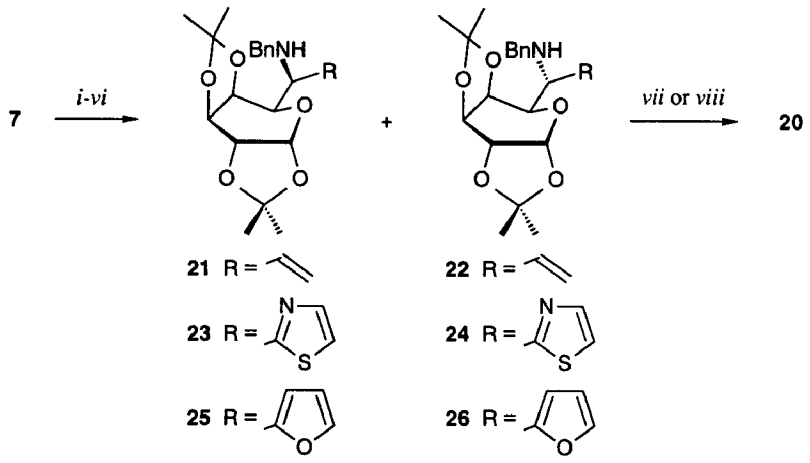
(*i*) $BnNH_2$, $MgSO_4$, $PhCH_3$, 12 h (98%); (*ii*) **1b**, $CeCl_3$, Et_2O, THF, -78°C → 0°C, 8 h (68%); (*iii*) CbzCl, 1,4-dioxane, H_2O, 0.5 h (**9**: 82%, **12**: 74%, **14**: 86%, **17**: 74%); (*iv*) KBr, AcO_2H, NaOAc, AcOH (**10**: 71%, **15**: 74%, **19**: 71%); (*v*) H_2, $Pd(OH)_2$, MeOH (**11**: 100%, **16**: 95%); (*vi*) **1b**, CuI, $BF_3{\cdot}Et_2O$, -70°C → -20°C, 6 h (70%); (*vii*) Ac_2O, dioxane, H_2O, 0.5 h (98%); (*viii*) DMSO, $(COCl)_2$, CH_2Cl_2, -60°C, 1 h then Et_3N, -60° → 0°C (93%).

organometallics derived from 2-thiazolyllithium, prepared by reaction of 2-bromothiazole with *n*-BuLi at low temperature (-78°C)[28], proved to be highly solvent-dependable. For

instance, the cerium-mediated addition in diethyl ether (entry 5) proceeded with the highest diastereoselectivity (ratio 5:1). Moreover, it is of interest to note that change of solvent to a mixture of diethyl ether/THF (entry 6) or pure THF (entry 7) had a detrimental effect on yield and stereoselectivity. On the contrary, THF is the solvent of choice for the copper-mediated *anti*-addition of thiazolyllithium to imine **7** with high stereoselectivity (entry 8), although the highest yield was found performing the latter condensation in diethyl ether (entry 9). These results support the earlier obtained findings (Chapter I) that hydroxymethylation of carbohydrate aldehydes in the less polar solvent diethyl ether shows enhanced α-chelation. On the contrary, exclusive Felkin-Anh type condensation to the *anti*-diastereomer is observed using THF as solvent. Finally, the nucleophilic addition of furyllithium, prepared by deprotonation of furan[29], was abortive (entry 10,11).

The diastereofacial selectivity of the vinyl- and thiazolyl-additions was unambiguously determined by conversion of the respective *anti*-adducts **22** and **24** to aldehyde **20** (Scheme 3). Thus, consecutive acetylation (Ac_2O, pyridine) and ozonolysis (O_3, CH_2Cl_2, MeOH, work-up Me_2S) of alkene **22** gave **20** in 61% overall yield. Similarly, acetylation of **24** followed by Dondoni's three-step one-pot demasking approach[30] (1. MeOTf, 2. $NaBH_4$, 3. $HgCl_2$) gave **20**, which was in all aspects identical to a previously prepared sample.

Scheme 3



Reagents and conditions

(*i*) $CH_2CHMgBr$, $CeCl_3$, Et_2O, THF, -78°C → 0°C, 8 h; (*ii*) $CH_2CHMgBr$, CuI, $BF_3{\cdot}Et_2O$, THF, -70°C → -20°C, 2 h; (*iii*) 2-thiazole-Li, $CeCl_3$, solvent, -78°C → 0°C, 8 h; (*ii*) 2-thiazole-Li, CuI, $BF_3{\cdot}Et_2O$, solvent, -70°C → -20°C, 3 h; (*v*) furyl-Li, $CeCl_3$, Et_2O, -78°C → 0°C, 8 h; (*vi*) furyl-Li, CuI, $BF_3{\cdot}Et_2O$, -70°C → -20°C, 3 h; (*vii*) (a) Ac_2O, pyridine, 1 h (78%) (b) O_3, MeOH, CH_2Cl_2, -78°C, 0.5 h, work-up Me_2S (77%); (*viii*) (a) Ac_2O, pyridine (92%) (b) MeOTf, CH_3CN (c) $NaBH_4$, MeOH (d) $HgCl_2$, CH_3CN, H_2O (72%).

Table 1. Copper- and cerium-mediated condensation of nucleophilic reagents with **3**.

Entry	Nucleophile	Solvent	Additive(s)	Product	Yield (%)	*syn* : *anti*
1	$PhMe_2SiCH_2MgCl$	THF/Et_2O	$CeCl_3$	**8**	68	>98 : <2
2		THF	$CuI/BF_3{\cdot}Et_2O$	**13**	70	<2 : >98
3	$CH_2CHMgCl$	THF/Et_2O	$CeCl_3$	**21**	61	>98 : <2
4		THF	$CuI/BF_3{\cdot}Et_2O$	**22**	61	<2 : >98
5	2-thiazolyl-Li	Et_2O	$CeCl_3$	**23+24**	57	5 : 1
6		THF/Et_2O	$CeCl_3$	**23+24**	35	3 : 1
7		THF	$CeCl_3$	**23/24**	0	-
8		THF	$CuI/BF_3{\cdot}Et_2O$	**24**	52	<2 : >98
9		Et_2O	$CuI/BF_3{\cdot}Et_2O$	**23+24**	70	1 : 5
10	furyl-Li	Et_2O	$CeCl_3$	**25/26**	0	-
11		THF	$CuI/BF_3{\cdot}Et_2O$	**25/26**	0	-

Conclusion

The results presented in this paper show that the compounds **12** and **20**, precursors of destomic acid and lincosamine, respectively, are readily obtained by cerium and copper mediated chain-extension of imine **7**. The *syn*- and *anti*-directed diastereoselective addition of organometallics to **7** may find general use for the future asymmetric synthesis of β-amino alcohols, which are key structural elements of nitrogen containing natural products, such as aminosugars, sphingolipid bases, amino acids and β-lactams.

Experimental

General methods and materials - Toluene was distilled from P_2O_5 and stored over 4Å molecular sieves, THF and Et_2O were freshly distilled from $LiAlH_4$. Methanol (HPLC-grade, Rathburn), 1,4-dioxane and acetic acid were used as received. All reactions were performed under strictly anhydrous conditions unless noted otherwise. Reactions were followed by TLC analysis on Schleicher and Schüll DC Fertigfolien F 1500 LS 254. Compounds were visualized by UV light (254 nm) followed by spraying with 20% sulfuric acid in MeOH and charring at 140°C, amines were charred with ninhydrin. Column chromatography was performed on silicagel 60, 230-400 mesh (Merck). Optical rotations were measured in $CHCl_3$ on a Propol automatic polarimeter. Mass spectra were recorded on a Finnigan MAT TSQ70 triple quadrupole mass spectrometer. ^1H NMR spectra and ^{13}C NMR spectra (50.1 MHz) were recorded using a Jeol JNM-FX 200 spectrometer, unless stated otherwise. ^1H NMR spectra (300 MHz) were recorded using a Bruker WM-300 spectrometer. Chemical shifts (δ) are given in ppm relative to tetramethylsilane as internal

standard. (Chloromethyl)dimethylphenylsilane, vinylmagnesium bromide and 2-bromothiazole were obtained from Aldrich Chemical Co. and used as received. *N*-sulfinyl *p*-toluenesulfonamide was prepared according to reference 18.

(Dimethylphenylsilyl)methylmagnesium chloride (1b, 1M in THF) - Under a stream of N_2, a small amount of a solution of (chloromethyl)dimethylphenylsilane **1a** (3.6 mL, 20.0 mmol) in THF (10 mL) was added to magnesium powder (0.53 g, 22 mmol) in a three-neck flask fitted with reflux condenser. The mixture was heated to reflux and the reaction was initiated with 1,2-dibromoethane (0.1 mL). The remaining solution of **1a** was added at such a rate as to remain a gentle reflux. After the exothermic reaction had subsided, THF (10 mL) was added and the grey-metallic solution was stirred at 40°C for an additional hour before cooling to rt.

6-(*p*-Tosylimino)-6-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (4) - To a cooled (-60°C) solution of oxalyl chloride (0.33 mL, 3.80 mmol) in CH_2Cl_2 (20 mL) was added dropwise a mixture of dimethylsulfoxide (0.44 mL, 6.3 mmol) in CH_2Cl_2 (6 mL). Subsequently, a solution of alcohol **2**[33] (0.65 g, 2.5 mmol) in CH_2Cl_2 (5 mL) was added dropwise and the reaction mixture was stirred at -60°C for 30 min. Et_3N (1.30 mL, 9.4 mmol) was added to the reaction mixture which was kept at -60°C for another 30 min before warming to rt. After 30 min, the mixture was diluted with CH_2Cl_2 (15 mL) and washed with H_2O (2x 5 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude aldehyde **3** thus obtained was dissolved in CH_2Cl_2 (2 mL) and, under a stream of argon, added dropwise *via* syringe to a cooled (0°C) solution of *N*-sulfinyl *p*-toluene-sulfonamide (0.81 g, 3.8 mmol) in CH_2Cl_2 (15 mL). After stirring for 14 h at rt, proton NMR analysis indicated no further conversion of **3** and ±80% formation tosylimine **4**. The imine thus obtained was used immediately in the next step. ^{1}H NMR: δ 8.46 (d, 1H, H-6, $J_{5,6}$ 3.3 Hz), 7.81 (d, 2H, H-arom, *J* 9.5 Hz), 7.29 (d, 2H, H-arom), 5.60 (d, 1H, H-1, $J_{1,2}$ 4.9 Hz), 4.64-4.21 (m, 4H, H-2, H-3, H-4, H-5), 1.49, 1.37, 1.33, 1.29 (4x s, CH_3, isoprop).

6,7-Dideoxy-7-dimethylphenylsilyl-1,2:3,4-di-*O*-isopropylidene-6-(*p*-tosylamino)-D/L-*glycero*-α-D-*galacto*-heptopyranose (5+6) - Under a stream of argon, there was added a 1M solution of Grignard **1b** in THF (10 mL) to a cooled (-20°C) solution of freshly prepared tosylimine **4** (2.5 mmol) in CH_2Cl_2 (15 mL). Stirring was continued at this temperature for 2 h, when TLC analysis (Et_2O/light petroleum, 3/1, v/v) indicated the complete disappearance of starting material. The mixture was quenched with NH_4Cl (100 mL, 15%), Et_2O (200 mL) was added and the mixture was transferred to a separatory funnel. The layers were separated, the organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residual oil was applied onto a column of silica gel and elution effected with Et_2O/light petroleum (1/3→1/2, v/v) to give, after concentration of the appropriate fractions, aminosilanes **5** and **6** as a mixture of diastereoisomers. Yield 1.52 g (53% from **2**). R_f 0.5 (Et_2O/light petroleum, 3/1, v/v). Compound **5**: $^{13}C\{^1H\}$ NMR: δ 141.9, 138.9, 138.7 (Cq, arom), 133.2-127.0 (CH, arom), 108.7, 107.9 (Cq, isoprop), 95.7 (C-1), 70.4-68.2 (C-2, C-3, C-4, C-5), 52.9 (C-6), 25.8, 25.5, 24.4, 23.5 (CH_3, isoprop), 21.1 (CH_3, Ts), 20.8 (C-7), -2.4, -2.9 ($SiCH_3$). Compound **6**: $^{13}C\{^1H\}$ NMR: δ 142.3, 139.2, 137.0 (Cq, arom), 133.5-127.0 (CH, arom), 109.0, 108.2 (Cq, isoprop), 95.7 (C-1), 70.6-68.2 (C-2, C-3, C-4, C-5), 51.7 (C-6), 25.7, 25.4, 24.3, 23.5 (CH_3, isoprop), 21.1 (CH_3, Ts), 18.6 (C-7), -1.9, -2.1 ($SiCH_3$).

6-Benzylimino-6-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (7) - Crude aldehyde **3**, prepared by Swern oxidation of **2**[33] (2.06 g, 8.0 mmol) as described in the synthesis of **4**, was dissolved in toluene (50 mL) and cooled to 0°C before $MgSO_4$ (2.40 g) and benzylamine

(1.31 mL, 12 mmol) were added. TLC analysis after 16 h (CH_2Cl_2/aceton/Et_3N, 95/5/1, v/v/v) showed the presence of one product. The reaction mixture was filtered, concentrated under reduced pressure and purified by silica gel flash chromatography using Et_2O/light petroleum/Et_3N (40/60/1→50/50/1→ 60/40/1, v/v). Concentration of the appropriate fractions afforded benzylimine **7** as a slightly yellow oil. Yield 2.72 g (98%). R_f 0.5 (CH_2Cl_2/aceton/Et_3N, 95/5/1, v/v/v). ^1H NMR: δ 7.75 (d, 1H, H-6, $J_{5,6}$ 3.9 Hz), 7.37-7.24 (m, 5H, H-arom), 5.61 (d, 1H, H-1, $J_{1,2}$ 4.9 Hz), 4.67-4.43 (m, 5H, H-3, H-4, H-5, CH_2, Bn), 4.34 (dd, 1H, H-2, $J_{2,3}$ 2.3 Hz), 1.53, 1.48, 1.34, 1.33 (4x s, 12H, CH_3, isoprop). ^{13}C NMR: δ 163.4 (C-6), 138.2 (Cq, arom), 127.9, 127.5, 126.5 (CH, arom), 108.9, 108.2 (Cq, isoprop), 95.7 (C-1), 72.9, 70.2, 70.0, 69.5 (C-2, C-3, C-4, C-5), 64.2 (CH_2, Bn), 25.6, 25.5, 24.5, 23.9 (CH_3, isoprop).

6-Benzylamino-6,7-dideoxy-7-dimethylphenylsilyl-1,2:3,4-di-*O*-isopropylidene-L-*glycero*-α-D-*galacto*-heptopyranose (8) - Under high vacuum (1 mmHg), $CeCl_3.7H_2O$ (1.86 g, 5.0 mmol) was dried at 140°C for 2 h. After cooling to rt, Et_2O (20 mL) was added and the resulting suspension was stirred overnight, followed by one hour ultrasonification. The mixture was cooled (0°C) and a solution of Grignard **1b** in THF (5 mL, 1M) was added slowly. After stirring for two hours at 0°C, the mixture was cooled to -78°C and a solution of freshly prepared imine **7** (0.69 g, 2.0 mmol) in THF (4 mL) was added dropwise. The mixture was kept at -78°C for another hour and the temperature was allowed to raise slowly to 0°C. The mixture was poured, with vigorous stirring, into a saturated solution of NaCl (30 mL), the layers were separated and the organic phase washed with H_2O (30 mL). The combined aqueous layers was extracted with Et_2O (2x 30 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Silica gel column chromatography (Et_2O) of the residual oil afforded pure aminosilane **8**. Yield 0.68 g (68%). R_f 0.1-0.2 (Et_2O/Et_3N, 99/1, v/v). $[\alpha]_D^{20}$ -50.2 (c 1.0). MS m/z: 498 $[M+H]^+$. ^1H NMR: δ 7.60-7.15 (m, 10 H, H-arom), 5.55 (d, 1H, H-1, $J_{1,2}$ 4.9 Hz), 4.56 (dd, 1H, H-3, $J_{2,3}$ 2.4 Hz, $J_{3,4}$ 7.9 Hz), 4.30 (dd, 1H, H-2), 4.28 (dd, 1H, H-4, $J_{4,5}$ 1.8 Hz), 3.77 (dd, 1H, H-5, $J_{5,6}$ 9.0 Hz), 3.63 (AB, 2H, CH_2, Bn, J -11.7 Hz), 3.22 (ddd, 1H, H-6, $J_{6,7a}$ 9.8 Hz, $J_{6,7b}$ 4.2 Hz), 1.80 (s, 1H, NH) 1.53, 1.40, 1.33, 1.21 (4x s, 12H, CH_3, isoprop), 1.40 (m, 1H, H-7a), 1.06 (m, 1H, H-7b), 0.40, 0.37 (2x s, 6H, $SiCH_3$). $^{13}C\{^1H\}$ NMR: δ 141.0, 140.1 (Cq, arom), 133.5-126.3 (CH, arom), 108.8, 108.1 (Cq, isoprop), 96.5 (C-1), 71.5, 71.1, 70.4, 69.6 (C-2, C-3, C-4, C-5), 53.4 (C-6), 47.6 (CH_2, Bn), 25.9, 24.7, 24.4 (CH_3, isoprop), 15.9 (C-7), -1.6, -2.2 ($SiCH_3$).

6-(*N*-Benzyloxycarbonyl)benzylamino-6,7-dideoxy-7-dimethylphenylsilyl-1,2:3,4-di-*O*-isopropylidene-L-*glycero*-α-D-*galacto*-heptopyranose (9) - Compound **8** (0.68 g, 1.37 mmol) was dissolved in a mixture of 1,4-dioxane (8 mL) and H_2O (4 mL). The solution was cooled (0°C) and treated with $NaHCO_3$ (0.25 g, 3.4 mmol) and benzyl chloroformate (0.26 mL, 1.5 mmol). After 5 min, the mixture was allowed to reach rt and stirred for 1 h. After this time, TLC analysis (Et_2O/light petroleum, 1/1, v/v) indicated the complete conversion of amine **8** into a more lipophilic product. The mixture was concentrated *in vacuo* and the residue was redissolved in Et_2O (20 mL) and extracted with H_2O (5 mL). The layers were separated and the organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash chromatography (Et_2O/light petroleum, 1/3→1/2→1/1, v/v) to give homogeneous **9**. Yield 0.71 g (82%). R_f 0.6 (toluene/EtOAc, 5/1, v/v). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 58°C): δ 140.0, 139.1 (Cq, arom), 133.5-126.7 (CH, arom), 109.1, 108.5 (Cq, isoprop), 96.7 (C-1), 71.5, 71.2, 70.2, 68.5 (C-2, C-3, C-4, C-5), 67.1 (CH_2, Cbz), 52.3 (C-6), 46.3 (CH_2, Bn), 25.9, 25.8, 24.9, 24.7 (CH_3, isoprop), 15.4 (C-7), -1.6, -2.2 ($SiCH_3$).

6-(*N*-Benzyloxycarbonyl)benzylamino-6-deoxy-1,2:3,4-di-*O*-isopropylidene-L-*glycero*-α-D-*galacto*-heptopyranose (10) - NaOAc (1.2 g, 14.6 mmol) was dissolved, with heating, in AcOH (10 mL) and the solution was added to aminosilane **9** (0.71 g, 1.12 mmol). KBr (0.16 g, 1.34 mmol) was added, the mixture was cooled to 10°C, and AcOOH (5.6 mL, 30% in acetic acid) was added dropwise under exclusion of light. During the addition gas was liberated. After stirring the reaction mixture for 1.5 h, TLC analysis (toluene/EtOAc, 5/1, v/v) indicated complete conversion of the starting material into a more hydrophilic product (R_f 0.37). The mixture was diluted with EtOAc (50 mL) and poured into a cooled (0°C) solution of $Na_2S_2O_3$ (10 mL, 15%). The layers were separated and to the organic phase was added a saturated solution of $NaHCO_3$ (15 mL), followed by solid $NaHCO_3$ until no more gas evolved. The organic phase was washed with H_2O (15 mL), dried ($MgSO_4$), filtered and solvents were evaporated under reduced pressure. The residue was redissolved in toluene (2x 5 mL) and concentrated. The oily product was applied onto a column of silica gel and elution was effected with a mixture of Et_2O/light petroleum (1/3→1/1, v/v). The appropriate fractions were collected and concentrated to give alcohol **10** as a colourless oil. Yield 0.41 g (71%). R_f 0.3 (toluene/EtOAc, 5/1, v/v). $[\alpha]_D^{20}$ -21.0 (c 1). ^{1}H NMR ($CDCl_3$, 58°C): δ 7.31-7.17 (m, 10H, H-arom), 5.50 (d, 1H, H-1, $J_{1,2}$ 4.9 Hz), 5.17 (s, 2H, CH_2, Cbz), 5.05-3.41 (m, 9H, H-2, H-3, H-4, H-5, H-6, H-7, CH_2, Bn), 1.46, 1.42, 1.30, 1.29 (4x s, 12H, CH_3, isoprop). ^{13}C{^{1}H} NMR ($CDCl_3$, 58°C): δ 157.8 (C=O), 137.9 (Cq, arom), 128.6-127.2 (CH, arom), 109.1, 108.8 (Cq, isoprop), 96.3 (C-1), 70.9, 70.8, 70.5, 65.6 (C-2, C-3, C-4, C-5), 67.3 (CH_2, Cbz), 63.5 (C-7), 55.0 (CH_2 Bn), 25.9, 25.6, 25.0, 24.4 (CH_3, isoprop).

6-Amino-6-deoxy-1,2:3,4-di-*O*-isopropylidene-L-*glycero*-α-D-*galacto*-heptopyranose (11) - Compound **10** (0.41 g, 0.80 mmol) was dissolved in dry MeOH (10 mL) and, under a N_2 atmosphere, $Pd(OH)_2$ (41 mg, 20% on carbon) was added. After applying a brief vacuum, the mixture was brought under a H_2-atmosphere (1 atm). After 4 h, **10** was completely converted into a more hydrophilic product (R_f 0.10). Hydrogen gas was removed by application of a brief vacuum and the suspension was filtrated over Celite. Solvents were evaporated to give crude amine **11** as a solid. Yield 0.23 g (100%). ^{13}C NMR: δ 108.9, 108.5 (Cq, isoprop), 96.0 (C-1), 71.1, 70.5, 70.3, 67.6 (C-2, C-3, C-4, C-5), 61.3 (C-7), 52.6 (C-6), 25.5, 24.6, 23.9 (CH_3, isoprop).

6-Amino-6-*N*-benzyloxycarbonyl-6-deoxy-1,2:3,4-di-*O*-isopropylidene-L-*glycero*-α-D-*galacto*-heptopyranose (12) - Amino alcohol **11** (0.23 g, 0.80 mmol) was treated with benzyl chloroformate as described for the preparation of **9** to give, after work-up and purification, urethane **12** as an oil. Yield 0.25 g (74%). R_f 0.3 (toluene/EtOAc, 3/2, v/v). $[\alpha]_D^{20}$ -46.4 (c 1)(Lit.[4a] -48.8°, Lit.[4b] -47.3). ^{1}H NMR: δ 7.40-7.26 (m, 5H, H-arom), 5.52 (d, 1H, H-1, $J_{1,2}$ 4.9 Hz), 5.10 (s, 2H, CH_2, Cbz), 4.63 (dd, 1H, H-3, $J_{2,3}$ 2.3 Hz, $J_{3,4}$ 8.1 Hz), 4.36 (dd, H-4, $J_{4,5}$ 1.6 Hz), 4.31 (dd, 1H, H-2), 4.11 (bd, 1H, H-5, $J_{5,6}$ 6.0 Hz), 3.90-3.71 (m, 3H, H-6, H-7), 1.58, 1.51, 1.43, 1.32 (4x s, 12H, CH_3, isoprop). ^{13}C{^{1}H} NMR: δ 156.1 (C=O), 136.4 (Cq, arom), 128.3, 127.8 (CH, arom), 109.2, 108.7 (Cq, isoprop), 96.4 (C-1), 71.0, 70.9, 70.8, 65.5 (C-2, C-3, C-4, C-5), 66.8 (CH_2, Cbz), 61.3 (C-7), 53.6 (C-6), 25.9, 25.8, 25.0, 24.1 (CH_3, isoprop).

6-Benzylamino-6,7-dideoxy-7-dimethylphenylsilyl-1,2:3,4-di-*O*-isopropylidene-D-*glycero*-α-D-*galacto*-heptopyranose (13) - To cooled (-40°C) Grignard reagent **1b** in THF (9.0 mL, 0.5 M) was added, under a stream of argon, copper(I) iodide (0.87 g, 4.5 mmol) with vigorous stirring. After 30 min, the mixture was cooled to -70°C and BF_3·Et_2O (0.56 mL, 4.5 mmol) was added. After 5 min, a solution of **7** (0.62 g, 1.8 mmol) in THF (3 mL) was added slowly to the mixture which was kept at -70°C for 1 h before slow warming to -20°C. The reaction was quenched with excess

Et_3N and poured into a vigorously stirred solution of 15% NH_4Cl (20 mL). Et_2O (50 mL) was added and the organic layer was washed with H_2O (15 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was applied onto a column of silica gel (elution: light petroleum followed by Et_2O/light petroleum/Et_3N, 20/80/1→40/60/1→60/40/1, v/v/v). Concentration of the appropriate fractions afforded **13**. Yield 0.63 g (70%). R_f 0.2 (CH_2Cl_2/ acetone/Et_3N, 95/5/1, v/v/v). $[\alpha]_D^{20}$ -34.0 (c 1). MS (m/z): 498 $[M+H]^+$. ^1H NMR: δ 7.58-7.10 (m, 10 H, H-arom), 5.56 (d, 1H, H-1, $J_{1,2}$ 4.9 Hz), 4.55 (dd, 1H, H-3, $J_{2,3}$ 2.0 Hz, $J_{3,4}$ 8.0 Hz), 4.46 (dd, 1H, H-4, $J_{4,5}$ 1.4 Hz), 4.27 (dd, 1H, H-2), 3.70 (AB, 2H, CH_2, Bn, J -12.6 Hz), 3.56 (dd, 1H, H-5, $J_{5,6}$ 7.7 Hz), 3.04 (m, 1H, H-6), 1.42 (dd, 1H, H-7a, $J_{6,7a}$ 5.1 Hz, $J_{7a,7b}$ 3.8 Hz), 0.95 (m, 1H, H-7b), 0.35, 0.31 ($SiCH_3$). ^{13}C NMR: δ 140.7, 139.8 (Cq, arom), 133.6-126.4 (CH, arom), 108.5, 107.8 (Cq, isoprop), 96.4 (C-1), 71.6, 70.9, 70.6 (C-2, C-3, C-4, C-5), 54.0 (C-6), 51.3 (CH_2, Bn), 19.2 (C-7), -1.8, -2.6 ($SiCH_3$).

6-(*N*-Benzyloxycarbonyl)benzylamino-6,7-dideoxy-7-dimethylphenylsilyl-1,2:3,4-di-*O*-isopropylidene-D-*glycero*-α-D-*galacto*-heptopyranose (14) - Compound **13** (0.63 g, 1.27 mmol) was converted to urethane **14** with benzyl chloroformate as described above for the synthesis of **9**. Yield 0.69 g (86%). R_f 0.5 (toluene/EtOAc, 5/1, v/v). $[\alpha]_D^{20}$ -38.8 (c 1). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 58°C): δ 139.7, 138.7 (Cq, arom), 133.7-126.5 (CH, arom), 109.0, 108.3 (Cq, isoprop), 96.6 (C-1), 71.4, 71.3, 70.0, 68.5 (C-2, C-3, C-4, C-5), 67.8 (CH_2, Cbz), 52.0 (C-6), 44.7 (CH_2, Bn), 26.1, 25.9, 24.9, 24.6 (CH_3, isoprop), 17.2 (C-7), -1.8, -2.2 ($SiCH_3$).

6-(*N*-Benzyloxycarbonyl)benzylamino-6-deoxy-1,2:3,4-di-*O*-isopropylidene-D-*glycero*-α-D-*galacto*-heptopyranose (15) - Oxidative demasking of **14** (0.47 g, 0.74 mmol) was executed as described for the preparation of **10** to give, after flash chromotography, alcohol **15** as an oil. Yield 0.28 g (74%). R_f 0.4 (toluene/EtOAc, 5/1, v/v). $[\alpha]_D^{20}$ -29.8). MS m/z: 513 $[M+H]^+$, 536 $[M+H]^+$. $^{13}C\{^1H\}$ NMR (58°C) δ: 157.3 (C=O), 137.1 (Cq, arom), 133.6, 128.4-127.0 (CH, arom), 108.9, 108.3 (Cq, isoprop), 96.6 (C-1), 71.3, 71.0, 70.0 (C-2, C-3, C-4, C-5), 63.2 (CH_2, Cbz), 55.3 (C-6), 45.3 (CH_2, Bn), 26.3, 26.0, 25.4 (CH_3, isoprop), 18.8 (C-7), -2.3, -2.7 ($SiCH_3$).

6-Amino-6-deoxy-1,2:3,4-di-*O*-isopropylidene-D-*glycero*-α-D-*galacto*-heptopyranose (16) - Compound **15** (0.28 g, 0.52 mmol) was hydrogenated as in the conversion **10**→**11** to give amine **16** as a solid after filtration and concentration. Yield 0.15 g (95%). R_f 0.3 (toluene/EtOAc, 3/2, v/v). ^{13}C NMR: δ 108.9, 108.3 (Cq, isoprop), 96.0 (C-1), 70.9, 69.9, 69.3, 67.8 (C-2, C-3, C-4, C-5), 66.5 (CH_2, Cbz), 63.0 (C-7), 52.2 (C-6), 25.7, 25.6, 24.4, 23.9 (CH_3, isoprop).

6-Amino-6-*N*-benzyloxycarbonyl-6-deoxy-1,2:3,4-di-*O*-isopropylidene-D-*glycero*-α-D-*galacto*-heptopyranose (17) - Amino alcohol **16** (0.15 g, 0.52 mmol) was treated with benzyl chloroformate as described for the preparation of **9** to give, after work-up and purification, urethane **17** as an oil. Yield 0.16 g (74%). R_f 0.3 (toluene/EtOAc, 3/2, v/v). $[\alpha]_D^{20}$ -45.1 (c 1)(Lit.[4a] -44.6). ^1H NMR: δ 7.36-7.26 (m, 5H, H-arom), 5.51 (d, 1H, H-1, $J_{1,2}$ 4.9 Hz), 5.10 (s, 2H, CH_2, Cbz), 4.60 (dd, 1H, H-3, $J_{2,3}$ 2.3 Hz, $J_{3,4}$ 7.9 Hz), 4.33 (dd, H-4, $J_{4,5}$ 0.8 Hz), 4.28 (dd, 1H, H-2), 3.90 (m, 2H, H-5, H-7a), 3.68 (m, 2H, H-6, H-7b), 2.40 (m, 1H, OH), 1.46, 1.33, 1.31 (3x s, 12H, CH_3, isoprop). $^{13}C\{^1H\}$ NMR: δ 156.1 (C=O), 136.4 (Cq, arom), 128.3, 127.8 (CH, arom), 109.2, 108.7 (Cq, isoprop), 96.3 (C-1), 71.0, 70.7, 70.5, 66.6 (C-2, C-3, C-4, C-5), 66.6 (CH_2, Cbz), 62.0 (C-7), 52.7 (C-6), 25.7, 24.8, 24.0 (CH_3, isoprop).

6-(*N*-benzyl)acetamido-6,7-dideoxy-7-dimethylphenylsilyl-1,2:3,4-di-*O*-isopropylidene-D-*glycero*-α-D-*galacto*-heptopyranose (18) - A solution of compound **13** (0.22 g, 0.42 mmol) in

pyridine (1.5 mL) and acetic anhydride (0.084 g, 0.90 mmol) was stirred at rt for 1 h. After TLC analysis (toluene/EtOAc, 3/2, v/v) revealed that the reaction had gone to completion, the reaction mixture was concentrated under reduced pressure, redissolved in toluene and concentrated again (3x 1 mL). The residue was applied onto a column of silica gel and elution was effected with toluene/EtOAc (49/1→8/1→7/3, v/v) to give pure **18**. Yield 0.24 g (98%). R_f 0.7 (toluene/EtOAc, 3/2, v/v). $[\alpha]_D^{20}$ -56.8 (c 2). ^{1}H NMR ($CDCl_3$, 58°C): δ 7.48-7.16 (m, 10H, H-arom), 5.45 (d, 1H, H-1, $J_{1,2}$ 4.9 Hz), 4.80 (m, 1H, H-3), 4.48-4.11 (m, 6H, H-2, H-4, H-6, CH_2, Bn), 3.60 (m, 1H, H-5), 1.92 (s, 3H, CH_3, Ac), 1.50 (m, 1H, H-7a), 1.49, 1.36, 1.28 (3x s, 12H, CH_3, isoprop), 1.10 (m, 1H, H-7b), 0.30 (s, 6H, $SiCH_3$). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 58°C): δ 171.3 (C=O), 137.0 (Cq, arom), 133.6-127.0 (CH, arom), 108.8, 108.3 (Cq, isoprop), 96.4 (C-1), 71.0, 70.7, 69.8 (C-2, C-3, C-4, C-5), 55.1 (C-6), 45.1 (CH_2, Bn), 26.2, 25.9, 25.2 (CH_3, isoprop), 23.4 (CH_3, Ac), 18.7 (C-7), -2.3, -2.6 ($SiCH_3$). IR (neat): 1640 $\nu.cm^{-1}$ (s, C=O, NAc, stretch).

6-(*N*-benzyl)acetamido-6-deoxy-1,2:3,4-di-*O*-isopropylidene-D-*glycero*-α-D-*galacto*-heptopyranose (19) - Oxidative unmasking of silane **18** (0.23 g, 0.42 mmol) was executed as described for the preparation of **10**. Pure **19** was obtained as an oil after purification. Yield 0.13 g (71%). R_f 0.2 (toluene/EtOAc, 1/1, v/v). $[\alpha]_D^{20}$ -33.4 (c 2). ^{1}H NMR ($CDCl_3$, 58°C): δ 7.30-7.13 (m, 10H, H-arom), 5.48 (d, 1H, H-1, $J_{1,2}$ 4.9 Hz), 4.60-3.63 (m, 9H, H-2, H-3, H-4, H-5, H-6, H-7, CH_2, Bn), 2.12 (s, 3H, CH_3, Ac), 1.49, 1.45, 1.31 (3x s, 12H, CH_3, isoprop), 1.10 (m, 1H, H-7b), 0.30 (s, 6H, $SiCH_3$). $^{13}C\{^1H\}$ NMR ($CDCl_3/CD_3OD$, 58°C): δ 171.3 (C=O), 139.0 (Cq, arom), 128.7-127.1 (CH, arom), 109.1, 108.8 (Cq, isoprop), 96.4 (C-1), 71.0, 70.9, 70.5, 69.9 (C-2, C-3, C-4, C-5), 63.1 (C-7), 58.9 (C-6), 45.5 (CH_2, Bn), 26.0, 25.9, 24.0 (CH_3, isoprop), 22.8 (CH_3, Ac).

6-(*N*-Benzyl)acetamido-6-deoxy-1,2:3,4-di-*O*-isopropylidene-D-*glycero*-α-D-*galacto*-heptodialdo-1,5-pyranose (20) - From **19**: Alcohol **19** (0.13 g, 0.30 mmol) was converted to aldehyde **20** as described for the oxidation of **2**. Pure **20** was obtained after purification by flash chromatography. Yield 0.12 g (93%). From **22**: Alkene **22** (0.30 g, 0.80 mmol) was acetylated as described in the preparation of **18**. The purified acetamide (0.26 g, 78%) was dissolved in CH_2Cl_2 (8 mL) and MeOH (2 mL) and cooled to -78°C. Through the solution was bubbled O_3 until the solution turned blue. Me_2S (5 mL) was added, the solution was stirred at -78°C an additional 20 min and allowed to reach rt. After careful removal of solvents and excess Me_2S under reduced pressure, the oily product was applied onto a column of silica gel (elution: toluene/EtOAc, 1/7→1/4, v/v) to obtain, after concentration of the approriate fractions, pure **20**. Yield 0.17 g (77%). From **24**: Thiazole **24** (0.20 g, 0.45 mmol) was acetylated as described in the preparation of **18**. The purified acetamide (0.20 g, 92%) was dissolved in anhydrous MeCN (5 mL) and activated powdered 4Å molecular sieves (1.0 g) and MeOTf (0.051 ml, 0.51 mmol) were added. The mixture was stirred for 15 min and concentrated to dryness. The residue was suspended in MeOH (5 mL), cooled (0°C) and treated with $NaBH_4$ (35 mg, 0.84 mmol). The mixture was stirred at rt for 20 min, diluted with acetone ((0.5 mL), filtered through Celite and concentrated. The residue was redissolved in 10:1 MeCN/H_2O (5 mL) and the solution was treated with $HgCl_2$ (0.11 g, 0.51 mmol) in 0.5 mL of the same solvent mixture. The mixture was stirred for 15 min, filtered through Celite and concentrated. The residue was partitioned between CH_2Cl_2 (20 mL) and aqueous KI (10 mL, 20%) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2x 10 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated. The oil thus obtained was purified by silica gel column chromatography as above to give **20**. Yield 0.13 g (77%). R_f 0.8 (CH_2Cl_2/EtOAc, 1/1, v/v). $[\alpha]_D^{20}$ -57.6 (c 1.5)(Lit.[26b] -56.1). ^{1}H NMR: δ 9.67 (s, 1H, H-7), 7.41-7.19 (m, 5H, H-arom), 5.52 (d, 1H, H-1, $J_{1,2}$ 4.9 Hz), 4.78 (dd, 1H, H-5, $J_{4,5}$ 7.8 Hz, $J_{5,6}$

9.0 Hz), 4.65 (AB, 2H, CH_2, Bn), 4.63 (dd, 1H, H-3, $J_{2,3}$ 2.4 Hz, $J_{3,4}$ 7.8 Hz), 4.33 (dd, 1H, H-2), 4.26 (dd, 1H, H-4), 3.58 (d, 1H, H-6), 2.11 (s, 3H, CH_3, Ac), 1.54, 1.46, 1.39, 1.32 (4x s, 12H, CH_3, isoprop). $^{13}C\{^1H\}$ NMR: δ 196.5 (C-7), 171.1 (C=O, Ac), 136.3 (Cq, arom), 128.6, 127.7, 127.3 (CH, arom), 109.3, 109.2 (Cq, isoprop), 96.5 (C-1), 70.8, 70.5, 64.2, 63.9 (C-2, C-3, C-4, C-5, C-6), 53.5 (CH_2, Bn), 25.9, 25.8, 25.0, 24.4 (CH_3, isoprop), 21.3 (CH_3, Ac). IR (neat): 1725 $v.cm^{-1}$ (s, C=O, C-7, stretch), 1640 (s, C=O, Ac, stretch).

6-Benzylamino-6-deoxy-7,8-dehydro-1,2:3,4-di-*O*-isopropylidene-α-L-*glycero*-D-*galacto*-octopyranose (21) - A solution of vinylmagnesium bromide in THF (5.6 mL, 1 M) was added dropwise to a cooled (-78°C) suspension of $CeCl_3$ (5.6 mmol), previously dried as in the preparation of **8**, in Et_2O (25 mL). The mixture was stirred for 1 h, then there was added dropwise *via* syringe a solution of freshly prepared **7** (0.97 g, 2.8 mmol) in Et_2O (15 mL). The residual slightly pink mixture was stirred for 1 h and slowly warmed to rt. Work-up was performed as described for **8** to give homogeneous **21** as a yellow oil. Yield 0.74 g (69%). R_f 0.2 (Et_2O/light petroleum, 3/1, v/v). $[\alpha]_D^{20}$ -36.0 (c 1). MS m/z: 375 $[M+H]^+$. ^1H NMR: δ 7.34-7.15 (m, 5H, H-arom), 5.72 (ddd, 1H, H-7, $J_{6,7}$ 9.7 Hz, $J_{7,8a}$ 17.9 Hz, $J_{7,8b}$ 10.2 Hz), 5.55 (d, 1H, H-1, $J_{1,2}$ 5.0 Hz), 5.42 (ddd, 1H, H-8a, $J_{8a,6}$ 0.8 Hz, $J_{8a,8b}$ 2.1 Hz), 5.29 (ddd, 1H, H-8b, $J_{8b,6}$ 0.6 Hz), 4.54 (dd, 1H, H-3, $J_{2,3}$ 2.3 Hz, $J_{3,4}$ 8.0 Hz), 4.28 (dd, 1H, H-2), 4.22 (dd, 1H, H-4, $J_{4,5}$ 1.7 Hz), 3.73 (AB, 2H, CH_2, Bn, J -14.4 Hz), 3.65 (ddd, H-5, $J_{5,6}$ 9.1 Hz), 3.45 (m, 1H, H-6), 2.34 (s, 1H, NH), 1.53, 1.42, 1.31, 1.30 (4x s, 12H, CH_3, isoprop). $^{13}C\{^1H\}$ NMR: δ 140.4 (Cq, arom), 136.2 (C-7), 127.9, 127.7, 126.2 (CH, arom), 118.9 (C-8), 108.6, 108.1 (Cq, isoprop), 96.1 (C-1), 70.8, 70.5, 69.8 (C-2, C-3, C-4, C-5), 60.1 (C-6), 50.6 (CH_2, Bn), 25.8, 25.7, 24.6, 24.1 (CH_3, isoprop).

6-Benzylamino-6-deoxy-7,8-dehydro-1,2:3,4-di-*O*-isopropylidene-α-D-*glycero*-D-*galacto*-octopyranose (22) - Vinylmagnesium bromide in THF (8.0 mL, 0.5 M) was cooled to -40°C and under a stream of argon, copper(I)iodide (0.75 g, 4.0 mmol) was added with vigorous stirring. After 30 min, the heterogeneous mixture was cooled to -70°C and $BF_3{\cdot}Et_2O$ (0.49 mL, 4.0 mmol) was added. After 5 min, a solution of **7** (0.69 g, 2.0 mmol) in THF (3 mL) was added slowly to the mixture which was kept at -70°C for 1 h before slow warming to -20°C. Work-up was executed as described for **13**. Purification on silica gel was performed with light petroleum followed by Et_2O/light petroleum/Et_3N (20/80/1→40/60/1→60/40/1, v/v/v). Concentration of the appropriate fractions afforded homogeneous **22**. Yield 0.45 g (61%). R_f 0.2 (Et_2O/light petroleum/Et_3N, 75/25/1, v/v/v). $[\alpha]_D^{20}$ -51.5 (c 2). MS (m/z): 375 $[M+H]^+$. ^1H NMR: δ 7.38-7.15 (m, 5H, H-arom), 5.76 (ddd, 1H, H-7, $J_{6,7}$ 7.8 Hz, $J_{7,8a}$ 10.4 Hz, $J_{7,8b}$ 18.2 Hz), 5.53 (d, 1H, H-1, $J_{1,2}$ 5.0 Hz), 5.26 (ddd, 1H, H-8a, $J_{8a,6}$ 0.7 Hz, $J_{8a,8b}$ 1.7 Hz), 5.22 (ddd, 1H, H-8b, $J_{8b,6}$ 0.9 Hz), 4.59 (dd, 1H, H-3, $J_{2,3}$ 2.3 Hz, $J_{3,4}$ 8.0 Hz), 4.50 (dd, 1H, H-4, $J_{4,5}$ 1.8 Hz), 4.28 (dd, 1H, H-2), 3.79 (AB, 2H, CH_2, Bn, J -14.3 Hz), 3.64 (dd, 1H, H-4, $J_{4,5}$ 1.7 Hz), 3.37 (tq, 1H, H-6), 1.62 (s, 1H, NH), 1.51, 1.43, 1.35, 1.31 (4x s, 12H, CH_3, isoprop). $^{13}C\{^1H\}$ NMR: δ 140.2 (Cq, arom), 137.7 (C-7), 127.9, 126.3 (CH, arom), 116.6 (C-8), 108.5, 107.8 (Cq, isoprop), 96.1 (C-1), 70.5, 70.4, 70.3, 69.7 (C-2, C-3, C-4, C-5), 59.3 (C-6), 50.6 (CH_2, Bn), 25.6, 24.5, 24.1 (CH_3, isoprop).

6-Benzylamino-6-deoxy-1,2:3,4-di-*O*-isopropylidene-6-(2-thiazolyl)-α-L-*glycero*-D-galactopyranose (23) - To a cooled (-78°C) solution of *n*-BuLi in hexanes (2.7 mL, 1.6 M) in Et_2O (6 mL) was added slowly, under an argon atmosphere, a solution of 2-bromothiazole (0.36 mL, 4.0 mmol) in Et_2O (6 mL) *via* syringe. The mixture was stirred at -78°C for 30 min and a purple solution was formed. The solution was added, *via* syringe, to a cooled (-78°C) suspension of $CeCl_3$ (4.0 mmol), previously dried as described for the synthesis of **8**. The mixture was stirred

at this temperature for 1 h, then there was added a solution of freshly prepared **7** (0.52 g, 1.5 mmol) in Et_2O (7 mL). The residual brown coloured solution was kept at -78°C for 1 h. After this time, TLC analysis (CH_2Cl_2/acetone, 95/5, v/v) revealed complete disappearance of **7** and the formation of a more hydrophilic product (R_f 0.5). The mixture was allowed to reach -20°C, diluted with Et_2O (50 mL) and poured into a saturated solution of NH_4Cl (30 mL, 15%). The layers were separated and the aqueous phase was extracted with Et_2O (30 mL). The combine organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was applied onto a column of silica gel and eluted with a mixture of Et_2O/light petroleum (33/66/1, v/v). Collection and concentration of the proper fractions afforded **23**, contaminated by approximately 20% of **24**, as an inseparable mixture of diastereomers. Yield 0.37 g (57%). R_f 0.5 (CH_2Cl_2/acetone/Et_3N, 95/5/1, v/v/v). ^1H NMR: δ 7.76 (d, 1H, H-4', thiazole, $J_{3',4'}$ 3.3 Hz), 7.33-7.19 (m, 6H, H-arom, H-3', thiazole), 5.56 (d, 1H, H-1, $J_{1,2}$ 4.9 Hz), 4.57 (m, 1H, H-5), 4.49 (d, 1H, H-3, $J_{3,4}$ 7.9 Hz), 4.29 (dd, 1H, H-2, $J_{2,3}$ 2.3 Hz), 4.10 (dd, 1H, H-4, $J_{4,5}$ 1.2 Hz), 3.95 (dd, 1H, H-6, $J_{5,6}$ 8.4 Hz), 3.74 (AB, 2H, CH_2, Bn, J -13.3), 2.30 (s, 1H, NH), 1.49, 1.47, 1.33, 1.30 (4x s, 12H, CH_3, isoprop). $^{13}C\{^1H\}$ NMR: δ 173.2 (C-1', thiazole), 142.3 (C-4', thiazole), 139.7 (Cq Bn), 127.9, 126.5 (CH, arom), 119.0 (C-3', thiazole), 109.0, 108.4 (Cq, isoprop), 96.3 (C-1), 70.8, 70.6, 70.5, 70.3 (C-2, C-3, C-4, C-5), 59.5 (C-6), 51.0 (CH_2, Bn), 25.7, 25.6, 24.7, 24.0 (CH_3, isoprop).

6-Benzylamino-6-deoxy-1,2:3,4-di-*O*-isopropylidene-6-(2-thiazolyl)-α-D-*glycero*-D-galactopyranose (24) - Under an argon atmosphere, 2-bromo-thiazole (0.27 mL, 3.0 mmol) in THF (10 mL) was added slowly *via* syringe to a cooled (-78°C) mixture of *n*-BuLi (2.1 mL, 1.6 M in hexanes) and THF (10 mL). The mixture was stirred at -78°C for 30 min, the temperature raised to -30°C and CuI (0.57 g, 3.0 mmol) and $BF_3.OEt_2$ (0.37 mL, 3.0 mmol) were added in analogous fashion as described earlier for the synthesis of **13**. At -70°C, freshly prepared imine **7** (0.35 g, 1.0 mmol) in THF (3 mL) was added slowly. The reaction mixture was stirred for 3h below -60°C. The reaction mixture was quenched with Et_3N (1 mL), diluted with Et_2O (40 mL) and NH_4Cl (5 mL) was added. After separation of the layers, the aqueous phase was extracted with Et_2O (2x 30 mL) and the combined organic layers extracted with brine (2x 5 mL). The organic phase was filtered, dried ($MgSO_4$) and solvents were evaporated to give a brown oil. Purification on silica gel (elution: Et_2O/light petroleum/Et_3N, 20/80/1→50/50/1, v/v/v) and concentration of the appropriate fractions afforded homogeneous **24**. Yield 0.22 g (52%). R_f 0.3 (CH_2Cl_2/acetone/Et_3N, 95/5/1, v/v/v). $[\alpha]_D^{20}$ -63.0 (c 2.0). ^1H NMR: δ 7.76 (d, 1H, H-4', thiazole, $J_{3',4'}$ 3.3 Hz), 7.48-7.15 (6H, H-arom, H-4', thiazole), 5.47 (d, 1H, H-1, $J_{1,2}$ 4.9 Hz), 4.61 (dd, 1H, H-3, $J_{2,3}$ 2.2 hZ, $J_{3,4}$ 7.9 Hz), 4.56 (dd, 1H, H-4, $J_{4,5}$ 1.7 Hz), 4.33 (m, 1H, H-5), 4.32 (d, 2H, CH_2, Bn, J -8.4 Hz), 4.28 (dd, 1H, H-2), 4.10 (ddd, 1H, H-6), 2.22 (s, 1H, NH), 1.50, 1.43, 1.34, 1.28 (4x s, 12H, CH_3, isoprop). $^{13}C\{^1H\}$ NMR: δ 172.6 (C-7), 141.9 (C-4', thiazole), 140.0 (Cq, arom), 128.2, 128.0, 127.9 (CH, arom), 119.0 (C-3', thiazole), 109.0, 108.4 (Cq, isoprop), 96.2 (C-1), 70.6, 70.5 (C-2, C-3, C-4, C-5), 59.7 (C-6), 51.9 (CH_2, Bn), 24.8, 24.7, 24.3, 24.2 (CH_3, isoprop).

References and notes

1. Published in part: van Delft, F.L.; de Kort, M.; van der Marel, G.A.; van Boom, J.H. *Tetrahedron: Asymmetry* **1994**, *5*, 2261.
2. (a) Boons, G.J.P.H.; van der Marel, G.A.; van Boom, J.H. *Tetrahedron Lett.* **1989**, *30*, 229. (b) Boons, G.J.P.H.; Overhand, M.; van der Marel, G.A.; van Boom, J.H. *Carbohydr. Res.* **1989**, *192*, c1-c4. (c) Boons, G.J.P.H.; Overhand, M.; van der Marel,

G.A.; van Boom, J.H. *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 1504. (d) Smid, P.; Noort, D.; Broxterman, H.J.G.; van Straten, N.C.R.; van der Marel, G.A.; van Boom, J.H. *Recl. Trav. Chim. Pays-Bas* **1992**, *111*, 524. (e) Smid, P.; Schipper, F.J.M.; Broxterman, H.J.G.; Boons, G.J.P.H.; van der Marel, G.A.; van Boom, J.H. *Recl. Trav. Chim. Pays-Bas* **1993**, *112*, 451. (f) Verduyn, R.; van Leeuwen, S.H.; van der Marel, G.A.; van Boom, J.H. *Recl. Trav. Chim. Pays-Bas* **1996**, *115*, 67.

3. Paulsen, H.; Pries, M.; Lorentzen, J.P. *Liebigs Ann. Chem.* **1994**, 389.
4. (a) Hashimoto, H.; Asano, K.; Fuji, F.; Yoshimura, J. *Carbohydr. Res.* **1982**, *104*, 87. (b) Gołebiowski, A.; Kozak, J.; Jurczak, J. *J. Org. Chem.* **1991**, *56*, 7344.
5. (a) Basile, T.; Bocoum, A.; Savoia, D.; Umani-Ronchi, A. *J. Org. Chem.* **1994**, *59*, 7766. (b) Wang, D.-K.; Dai, L.-X.; Hou, X.-L. *Tetrahedron Lett.* **1995**, *36*, 8649. (c) Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Raimondi, L. *Tetrahedron* **1994**, *50*, 9471. (d) Cativiela, C.; Díaz-de-Villegas, M.D.; Gálvez, J.A. *Tetrahedron Lett.* **1995**, *36*, 2859.
6. (a) Inoue, I.; Shindo, M.; Koga, K.; Tomioka, K. *Tetrahedron* **1994**, *50*, 4429. (b) Denmark, S.E.; Nakajima, N.; Nicaise, O.J.-C. *J. Am. Chem. Soc.* **1994**, *116*, 8797. (c) Hashimoto, Y.; Takaoki, K.; Sudo, A.; Ogasawara, T.; Saigo, K. *Chem. Lett.* **1995**, 235.
7. Organocopper reagents: (a) Wada, M.; Sakurai, Y.; Akiba, K. *Tetrahedron Lett.* **1984**, *25*, 1079. (b) Matsumoto, T.; Kobayashi, Y.; Takemoto, Y.; Ito, Y.; Kamijo, T.; Harada, H.; Terashima, S. *Tetrahedron Lett.* **1990**, *31*, 4175. Organozinc reagents: (c) Mukaiyama, T.; Goto, Y.; Shoda, S. *Chem. Lett.* **1983**, 671. Organolanthanides: (d) Reetz, M.T.; Jaeger, R.; Drewlies, R.; Hübel, M. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 103. (e) Franz, T.; Hein, M.; Veith, U.; Jäger, V.; Peters, E.-M.; Peters, K.; von Schnering, H.G. *ibid.* **1994**, *33*, 1298. (f) Matsubara, S.; Ukita, H.; Kodama, T.; Utimoto, K. *Chem. Lett.* **1994**, 831. (g) Heuschman, M.; Betz, J. *Tetrahedron Lett.* **1995**, *36*, 4043. See also references 7b, 9a-c and 10. Grignard and organolithium reagents: (h) Veith, U.; Leurs, S.; Jäger, V. *J. Chem. Soc., Chem. Commun.* **1996**, 329.
8. Other examples using Lewis acids: (a) Volkmann, R.A.; Davis, J.T.; Meltz, C.N. *J. Am. Chem. Soc.* **1983**, *105*, 5946. (b) Brook, M.A.; Jahangir *Synth. Commun.* **1988**, *18*, 893.
9. (a) Denmark, S.E.; Edwards, J.P.; Nicaise, O. *J. Org. Chem.* **1993**, *58*, 569. (b) Enders, D.; Reinhold, U. *Synlett* **1994**, 792. (c) Enders, D.; Reinhold, U. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1219. (d) Alexakis, A.; Lensen, N.; Tranchier, J.-P.; Mangeney, P.; Feneau-Dupont, J.; Declercq, J.P. *Synthesis* **1995**, 1038. (e) Enders, D.; Reinhold, U. *Liebigs. Ann. Chem.* **1996**, 11.
10. (a) Ukaji, Y.; Kume, K.; Watai, T.; Fujisawa, T. *Chem. Lett.* **1991**, 173. (b) Karl Dieter, R.; Datar, R. *Can. J. Chem.* **1993**, *71*, 814. (c) Greven, R.; Jütten, P.; Scharf, H.-D. *J. Org. Chem.* **1993**, *58*, 3742. (d) Greven, R.; Jütten, P.; Scharf, H.-D. *Carbohydr. Res.* **1995**, *275*, 83.
11. (a) Basha, A.; Henry, R.; McLaughlin, M.A.; Ratajczyk, J.D.; Wittenberger, S.J. *J. Org. Chem.* **1994**, *59*, 6103. (b) Giovannini, R.; Marcantoni, E.; Petrini, M. *ibid.* **1995**, *60*, 5706. (c) Dondoni, A.; Junquera, F.; Merchan, F.L.; Merino, P.; Tejero, T. *J. Chem. Soc., Chem. Commun.* **1995**, 2127.
12. (a) Davis, F.A.; Giangiordano, M.A.; Starner, W.E. *Tetrahedron Lett.* **1986**, *34*, 3957. (b) Sisko, J.; Weinreb, S.M. *J. Org. Chem.* **1990**, *55*, 393.
13. (a) Itsuno, S.; Yanaka, H.; Hachisuka, C.; Ito, K. *J. Chem. Soc., Perkin Trans. 1* **1991**,

1341. (b) Bongini, A.; Camerini, R.; Hofman, S.; Panunzio, M. *Tetrahedron Lett.* **1994**, *35*, 8045. (c) Cainelli, G.; Giacomini, D.; Walzl, M. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2150.
14. Giuliano, R.M.; Manetta, V.E.; Smith, G.R. *Carbohydr. Res.* **1995**, *278*, 345 and references cited therein.
15. Wutz, P.G.M.; Jung, Y.W. *Tetrahedron Lett.* **1986**, *27*, 2079 and references cited.
16. Collado, I.; Ezquerra, J.; Pedregal, C. *J. Org. Chem.* **1995**, *60*, 5011 and references cited therein.
17. (a) Katritzky, A.R.; Hong, Q.; Yang, Z. *J. Org. Chem.* **1994**, *59*, 7947. (b) Katritzky, A.R.; Hong, Q.; Yang, Z. *ibid.* **1995**, *60*, 3405.
18. Kim, Y.H.; Shin, J.M. *Tetrahedron Lett.* **1985**, *26*, 3821.
19. Aldimines normally adopt the (*E*)-configuration: McCarty, C.G. in *Chemistry of the Carbon-Nitrogen Double Bond*, Patai, S., Ed.; Interscience: London, 1970; pp 363.
20. (a) Imamoto, T.; Kusumoto, T.; Yokoyama, M. *J. Chem. Soc., Chem. Commun.* **1982**, 1042. (b) Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392. (c) T. Imamoto, in *Comprehensive Organic Synthesis* Trost, B.M., Fleming, I., Eds.; Pergamon Press, Oxford, 1991, Vol 3, pp 231.
21. An electronegative protective group at the amine function is required to avoid N-oxidation during unmasking of the silyl moiety.
22. Fleming, I.; Sanderson, P.E.J. *Tetrahedron Lett.* **1987**, *28*, 4229.
23. Cram, D.J.; Abd Elhafez, F.A. *J. Am. Chem. Soc.* **1952**, *74*, 5828.
24. In this respect, it of interest to note that the trans geometry of the C=N double bond forces the $Ce(III)Cl_3$ to coordinate cis to the sugar moiety.
25. Hoeksema, H.; Bannister, B.; Birkenmeyer, R.D.; Kagan, F.; Magerlein, B.J.; MacKellar, F.A.; Schroeder, W; Slomp, G; Herr, R.R. *J. Am. Chem. Soc.* **1964**, *86*, 4223. For a review: Gołebiowski, A.; Jurczak, J. *Total Synthesis of Lincomycin and Related Chemistry* in *Recent Progress in the Chemical Synthesis of Antibiotics*, Lukacs, G.; Ohno, M., Eds.; Springer Verlag: Berlin-Heidelberg, 1990; pp 365.
26. (a) Atsumi, T.; Fukumaru, T.; Ogawa, T.; Matsui, M. *Agr. Biol. Chem.* **1973**, *37*, 2621. (b) Dondoni, A.; Franco, S.; Merchan, F.; Merino, P.; Tejero, T. *Synlett* **1993**, 78.
27. (a) Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199. (b) Anh, N.T.; Eisenstein, O. *Nouv. J. Chem.* **1977**, *1*, 61.
28. (a) Dondoni, A.; Perrone, D. *Synthesis* **1993**, 1162. (b) Dondoni, A.; Merino, P. *Org. Synth.* **1993**, *72*, 21.
29. For instance, see: Martin, S.F.; Chen, H.-J.; Lynch, V.M. *J. Org. Chem.* **1995**, *60*, 276.
30. Conversion of alkenes to aldehydes is readily executed by ozonolysis. For unmasking of the 2-thiazole function to the corresponding aldehyde see: Dondoni, A.; Marra, A.; Perrone, D. *J. Org. Chem.* **1993**, *58*, 275. See also reference 28.
31. Dondoni, A.; Junquera, F.; Merchan, F.L.; Merino, P.; Tejero, T. *Synthesis* **1994**, 1451 and references cited therein.
32. The preparation of organocerium reagents from Grignard reagents usually proceeds at 0°C. However, the preparation of the vinylcerium reagent is executed at -78°C in order to avoid decomposition. See reference 20b.
33. Tipson, R.S. *Methods Carbohydr. Chem.* **1963**, *2*, 246.

IV

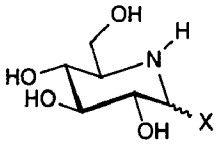
Stereocontrolled Hydroxymethylation of Carbohydrate Imines: Synthesis of 1-Deoxy Azasugars[1]

Abstract

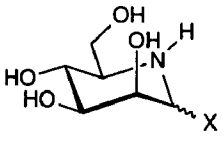
Nucleophilic hydroxymethylation of the readily accessible furanoside imines **8-10**, using an organocopper or organocerium reagent derived from (chloromethyl)dimethylphenylsilane (**4a**), proceeds with high diastereoselectivity to give the respective *anti*- and *syn*-β-amino silane adducts. Further processing of the appropriate diastereomers gives access to the glucosidase inhibitors nojirimycin (**1a**), mannojirimycin (**2a**) and galactostatin (**3a**), as well as the 1-deoxy analogues **1b-3b**.

Introduction

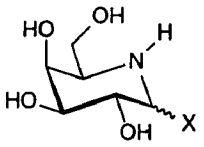
The azasugars nojirimycin (**1a**), mannojirimycin (**2a**), galactostatin (**3a**), as well as the corresponding 1-deoxy analogues **1b-3b** have attracted considerable interest as glycosidase inhibitors[2]. Structurally, the 1-deoxy compounds **1b-3b** are stable analogues of the relatively unstable[3] hemiaminals **1a-3a**, which are pyranose sugars having an amino function at the position of the ring oxygen. The high promise of glucosidase inhibitors as potential drugs for treatment of diabetes[4], cancer[5] and viral infections[6] led to a plethora of



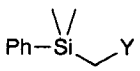
1a X = OH
b X = H



2a X = OH
b X = H



3a X = OH
b X = H



4a Y = Cl
b Y = MgCl
c Y = $SnBu_3$
d Y = Li

chemical approaches[7-9] towards the compounds **1-3**. For example, contributions from our laboratory[10-12] revealed that 1-deoxynojirimycin (**1b**) and 1-deoxymannojirimycin (**2b**) are readily accessible *via* double Walden inversion at C-5 of D-glucofuranose[10a] and D-mannofuranose[10b] derivatives, respectively. Polyhydroxylated pyrrolidines, *i.e.* furanose 1-deoxy azasugars, were prepared[11] *via* nucleophilic opening of 1,4-cyclic sulfates of arabinitol and xylitol. Recently, it was revealed that diastereoselective chain-extension of a suitably protected D-*xylo* aldehyde, using the hydroxymethylating reagent **4b**, afforded[12], after introduction of an amino function, a known precursor of **1**. This Chapter deals with a more effective approach towards the preparation of 1-deoxy azasugars **1b-3b** entailing nucleophilic hydroxymethylation of carbohydrate imines.

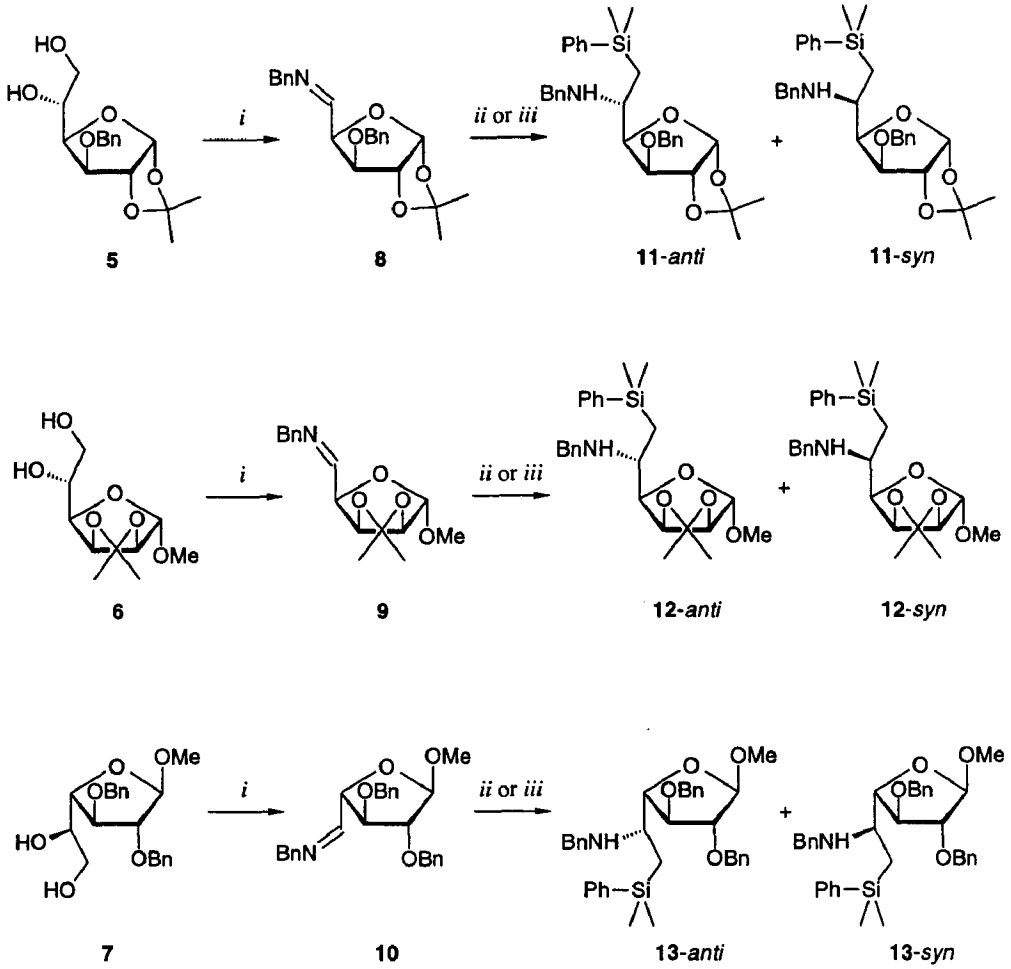
Earlier we reported[13] (see Chapter I) that hydroxymethylation of a benzylimino derivative of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose with Grignard reagent **4b** proceeds smoothly under the influence of $CuI/BF_3{\cdot}Et_2O$ or $CeCl_3$, to give the respective *anti*- and *syn*-β-amino silane adducts with excellent diastereoselectivity. The latter adducts were converted into known precursors of lincosamine and destomic acid, carbohydrate components of the antibiotics lincomycin and destomycin, respectively. Accordingly, it was envisaged that hydroxymethylation of the readily available imino sugars **8-10** would lead to the formation of the individual diastereomers of β-amino silanes **11-13** which in turn may give access to target compounds **1a-3a** and the 1-deoxy analogues **1b-3b**.

The requisite sugars **5**, **6** and **7** (Scheme 1) were prepared *via* known procedures from D-glucose, D-mannose and D-galactose. Thus, benzylation and selective deacetonation of commercially available 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose gave **5**[14]. Mannofuranoside **6** was prepared[15] in a one-pot two-step procedure involving acid treatment of D-mannose in a mixture of methanol and acetone followed by selective deacetonation. The dibenzylated galactose derivative **7** was accessible[16] by sequential Fisher methylation, selective acetonation, benzylation and finally isopropylidene removal.

Conversion of the resulting diols **5-7** into the respective benzylimines **8-10** was effected in two steps. Oxidative cleavage with sodium periodate, followed by treatment of the resulting aldehyde with benzylamine and $MgSO_4$ gave the isomerically pure[17] (E)-imines **8-10**. Hydroxymethylation of the individual imines was executed under the influence of $CuI/BF_3{\cdot}Et_2O$ and $CeCl_3$, the results of which are summarized in Table 1. Precomplexation[18] of Grignard reagent **4b** with CuI (-40°C) and $BF_3{\cdot}Et_2O$ (-70°C) was followed by slow addition of the freshly prepared imine (*i.e.* **8**, **9** or **10**). The reaction mixture was stirred at -70°C for one hour and quenched with aqueous NH_4Cl. Purification by silica gel column chromatography afforded the adducts **11**-*anti* (entry 1) and **12**-*anti* (entry 3) with excellent diastereoselectivity. On the other hand, copper-mediated hydroxymethylation of L-*arabino* imine **10** (entry 5) resulted in an inseparable mixture of the *anti*- and *syn*-epimers of **13**.

The cerium-mediated hydroxymethylation of **8-10** with the organocerium compound derived from Grignard reagent **4b** was not successful, only a small amount (<5% yield) of

Scheme 1



Reagents and conditions

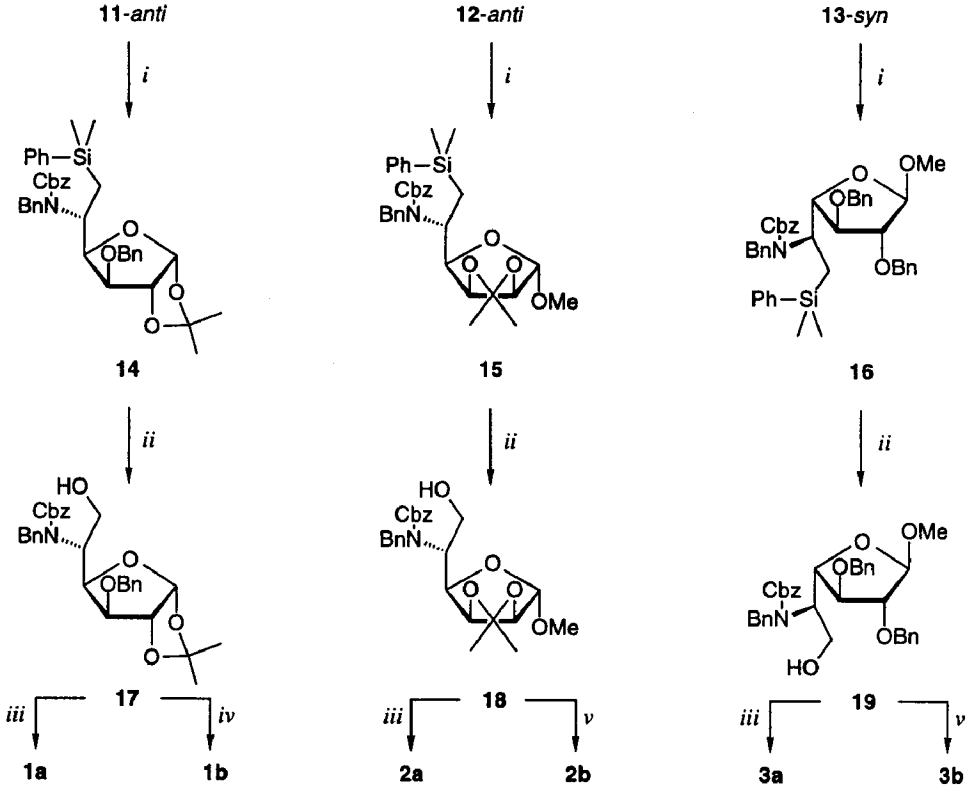
(*i*) (a) $NaIO_4$, MeOH, H_2O, 30 min (b) $BnNH_2$, $MgSO_4$, $PhCH_3$, 16 h (**8**: 84%, **9**: 86%, **10**: 67%); (*ii*) **4b**, CuI, $BF_3{\cdot}Et_2O$, THF, -70°C → -20°C; (*iii*) **4d**, $CeCl_3$, THF/Et_2O, -78°C → rt.

the adducts could be isolated. Fortunately, precomplexation of $CeCl_3$ with the organolithium analogue **4d**, obtained[19] *in situ* by transmetallation of stannane derivative **4c**[20] with *n*-butyllithium (0°C), proved to be more successful. Thus, addition at low temperature (-78°C) of a solution of imines **8-10** to the organocerium reagent resulted in the formation of the respective β-amino silane adducts **11-13**, albeit with variable yields and stereoselectivity (entry 2,4,6). As can be seen in Table 1, the addition of **4d** to D-*xylo* imine **8** (entry 2) as well as to D-*lyxo* imine **9** (entry 4) proceeded with lower diastereoselectivity. In contrast, hydroxymethylation of **10** (entry 6) led to the exclusive formation of the **13**-*syn* diastereomer, *i.e.* the *anti*-isomer could not be detected by ^1H

NMR analysis. The latter results indicate that the cerium-mediated addition largely depends on the organometallic nature of the starting hydroxymethylating reagent, implying that the organocerium compound may not exist as σ-bonded $PhMe_2SiCH_2$-$CeCl_2$ but rather[21] in the form of a weakly associated species $PhMe_2SiCH_2MgCl$·$CeCl_3$ or $PhMe_2SiCH_2Li$·$CeCl_3$. It has also been suggested[22] that the cerium salt may only serve as a strongly aminophilic Lewis acid.

The diastereomerically pure adducts **11**-*anti*, **12**-*anti* and **13**-*syn* were transformed into suitable precursors of azasugars **1-3** *via* previously described[13] routes (Scheme 2). Thus, protection of the benzylamino with benzyl chloroformate under Schotten-Baumann conditions ($NaHCO_3$, 1,4-dioxane, H_2O) to the respective urethanes **14**, **15** and **16** was followed by oxidative unmasking of the silyl moiety with potassium bromide in the presence of peracetic acid, to afford the primary alcohols **17-19** in good yields. The

Scheme 2



Reagents and conditions

(*i*) CbzCl, $NaHCO_3$, 1,4-dioxane, H_2O, 30 min (**14**: 91%, **15**: 79%, **16**: 85%); (*ii*) KBr, NaOAc, AcO_2H, AcOH (**17**: 70%, **18**: 76%, **19**: 66%); (*iii*) (a) H_2, $Pd(OH)_2$, MeOH (b) SO_2, H_2O (c) Dowex-1X8 (OH^-) (**1a**: 71%); (*iv*) (a) 80% TFA, 20 min (b) H_2, $Pd(OH)_2$, AcOH, H_2O, MeOH (84%); (*v*) (a) 80% AcOH, 100°C, 6 h (b) H_2, $Pd(OH)_2$, AcOH, H_2O, MeOH (**2b**: 86%, **3b**: 65%).

Table 1. Copper(I) or cerium(III)-mediated hydroxymethylation of imines **8-10**.

Entry	Imine	Conditions[a]	Adduct	Yield (%)	*anti* : *syn*
1	**8**	A	**11**	54	>98 : <2
2		B		19	2 : 5
3	**9**	A	**12**	76	>98 : <2
4		B		49	1 : 9
5	**10**	A	**13**	73	5 : 2
6		B		57	<2 : >98

[a]A: **4b**, $CuI/BF_3{\cdot}Et_2O$, -70°C → -20°C, B: **4d**, $CeCl_3$, -78°C → rt

conversion of **17** into **1a** was executed following a general and well-established procedure[7b] devised for the preparation of azasugars. Thus, reductive removal of benzyl protective groups in **17** with $Pd(OH)_2$, followed by treatment with SO_2 and basic hydrolysis of the resulting bisulfite adduct, gave **1a**[7b,23] as a mixture of anomers. It is evident that conversion of **18** and **19** by a similar sequence of events will give access to compounds **2a** and **3a**, respectively. On the other hand, deacetonation of **17** prior to hydrogenation led to **1b**[8]. In a similar fashion, alcohols **18** and **19** were converted into 1-deoxymannojirimycin (**2b**)[9] and galactostatin (**3b**)[10].

Conclusion

Hydroxymethylation of carbohydrate imines under the influence of $CuI/BF_3{\cdot}Et_2O$ or $CeCl_3$ proceeds with high stereoselectivity. The Grignard reagent **4b** is most suitable for *anti*-additions using copper(I) iodide and $BF_3{\cdot}Et_2O$, whereas the best results for cerium-mediated addition can be obtained by application of the organolithium derivative **4d**. The results presented in this Chapter indicate (see also Chapter III, V and VI) that the cerium or copper-mediated chain-extension of α-alkoxy imines may be a valuable asset in the future preparation of chiral 1,2-amino alcohols.

Experimental

General methods and materials - Toluene was distilled from P_2O_5 and stored over 4Å molecular sieves, THF and Et_2O were freshly distilled from $LiAlH_4$. Methanol (HPLC-grade, Rathburn), 1,4-dioxane and AcOH were used as received. All reactions were performed under strictly anhydrous conditions unless noted otherwise. Reactions were followed by TLC analysis on Schleicher and Schüll DC Fertigfolien F 1500 LS 254. Compounds were visualized by UV light (254 nm) and by spraying with 20% sulfuric acid in MeOH followed by charring at 140°C. Column chromatography was performed on silica gel 60, 230-400 mesh (Merck). ^1H NMR spectra and ^{13}C NMR spectra (50.1 MHz) were recorded in $CDCl_3$ using a Jeol JNM-FX 200 spectrometer,

unless stated otherwise. ^{1}H NMR spectra (300 MHz) were recorded using a Bruker WM-300 spectrometer. Chemical shifts (δ) are given in ppm relative to tetramethylsilane as internal standard. Optical rotations were measured in $CHCl_3$ on a Propol automatic polarimeter. Mass spectra were recorded on a Finnigan MAT TSQ70 triple quadrupole mass spectrometer. (Chloromethyl)dimethylphenylsilane was obtained from Aldrich Chemical Co. and used as received.

3-*O*-Benzyl-5-benzylimino-5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose (8) - To a rapidly stirred solution of **5**[14] (3.10 g, 10.0 mmol) in MeOH (50 mL) at 0°C was added a solution of $NaIO_4$ (4.39 g, 21.0 mmol) in H_2O (10 mL). The solution was stirred for 1 h at room temperature, after which time TLC analysis (Et_2O/light petroleum, 3/1, v/v) showed complete conversion of starting material into a lipophilic product (R_f 0.4-0.8). The reaction mixture was filtered, diluted with CH_2Cl_2 (50 mL) and washed with H_2O (10 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. After coevaporation of the residue with toluene (2x 4 mL), it was dissolved in the same solvent (30 mL), cooled (0°C) and $MgSO_4$ (1.32 g) and $BnNH_2$ (1.20 mL, 11 mmol) were added. After 16 h, the reaction mixture was filtered and concentrated under reduced pressure. The crude oil thus obtained was purified by flash chromatography on silica gel to give **8**. Yield 3.08 g (84%). R_f 0.4-0.8 (Et_2O/light petroleum/Et_3N, 75/25/1, v/v/v). ^{1}H NMR: δ 7.83 (dt, 1H, H-5, $J_{4,5}$ 5.1 Hz, $J_{5,Bn}$ -1.5 Hz), 7.29-7.17 (m, 10H, H-arom), 6.05 (d, 1H, H-1, $J_{1,2}$ 4.7 Hz), 4.77 (dd, 1H, H-4, $J_{3,4}$ 3.5 Hz), 4.67 (d, 1H, H-2), 4.66 (d, 2H, CH_2, NBn), 4.53 (AB, 2H, CH_2, OBn, J -12.3), 4.16 (d, 1H, H-3), 1.46, 1.32 (2x s, 6H, isoprop). ^{13}C{^{1}H} NMR: δ 162.4 (C-5), 138.0, 137.0 (Cq, arom), 128.3-126.9 (CH, arom), 111.8 (Cq, isoprop), 105.4 (C-1), 84.1, 82.4, 81.5 (C-2, C-3, C-4), 71.9 (CH_2, OBn), 64.7 (CH_2, NBn), 26.6, 26.2 (CH_3, isoprop).

3-*O*-Benzyl-5-benzylamino-5,6-dideoxy-6-dimethylphenylsilyl-1,2-*O*-isopropylidene-α-D-glucofuranose (11-*anti*) - Under an argon atmosphere, magnesium (0.13 g, 5.5 mmol) in refluxing THF (3 mL) was activated by the addition of 1,2-dibromoethane (0.1 mL). Next, (chloromethyl)dimethylphenylsilane (0.92 mL, 5.0 mmol) in THF (4 mL) was added and the temperature was kept at 50°C for one hour, before dilution with THF (5 mL) and cooling to -30°C. Under a stream of argon, solid CuI (0.95 g, 5.0 mmol) was added and stirring was continued for 10 min before further cooling (-70°C) and the addition of $BF_3{\cdot}Et_2O$ (0.62 mL, 5.0 mmol). The resulting suspension was stirred for 5 min, then benzylimine **8** (0.73 g, 2.5 mmol) in THF (4 mL) was added slowly *via* syringe. The reaction mixture was stirred for 1 h at -70°C before slow warming to -20°C, quenching with Et_3N (1.0 mL) and addition of aqueous NH_4Cl (5 mL, 15%). Extraction with Et_2O (2x 35 mL) and concentration of the combined organic layers, dried over $MgSO_4$, gave a syrup which was applied onto a column of silica gel. Elution was effected with light petroleum/Et_3N (99/1, v/v), followed by Et_2O/light petroleum/Et_3N (4/95/1→19/80/1, v/v/v). Concentration of the appropriate fractions gave compound **11**-*anti*. Yield 0.56 g (54%). R_f 0.5 (Et_2O/light petroleum/Et_3N, 75/25/1). $[\alpha]_D^{20}$ -34.0 (c 1.0). MS (m/z): 518 $[M+H]^+$. ^{1}H NMR (300 MHz): δ 7.54-7.03 (m, 15H, H-arom), 5.93 (d, 1H, H-1, $J_{1,2}$ 3.9 Hz), 4.61 (d, 1H, H-2), 4.56 (AB, 2H, CH_2, OBn, J -11.7 Hz), 4.06 (dd, 1H, H-4, $J_{3,4}$ 3.1 Hz, $J_{4,5}$ 7.4 Hz), 4.01 (d, 1H, H-3), 3.66 (AB, 2H, CH_2, NBn, J -12.7 Hz), 3.30 (ddd, 1H, H-5, $J_{5,6a}$ 5.0 Hz, $J_{5,6b}$ 8.8 Hz), 1.49, 1.33 (2x s, 6H, CH_3, isoprop), 1.28 (dd, 1H, H-6a, $J_{6a,6b}$ -15.0 Hz), 1.13 (dd, 1H, H-6b), 0.34 (s, 6H, $SiCH_3$). ^{13}C{^{1}H} NMR: δ 140.6, 139.7, 137.1 (Cq, arom), 133.3, 128.4-126.3 (CH, arom), 110.8 (Cq, isoprop), 104.3 (C-1), 84.0, 81.7, 81.6 (C-2, C-3, C-4), 71.1 (CH_2, OBn), 52.6 (C-5), 51.0 (CH_2, NBn), 26.5, 26.0 (CH_3, isoprop), 19.5 (C-6), -2.0, -2.1 ($SiCH_3$).

3-*O*-Benzyl-5-benzylamino-5,6-dideoxy-6-dimethylphenylsilyl-1,2-*O*-isopropylidene-β-L-idofuranose (11-*syn*) - Under high vacuum (1 mmHg), $CeCl_3.7H_2O$ (1.49 g, 4.0 mmol) was dried at 140°C for 2 h. After cooling to room temperature, Et_2O (20 mL) was added and the resulting suspension was stirred overnight, followed by one hour ultrasonification. The mixture was cooled (-78°C) and there was added a solution of organolithium reagent **4b**, prepared by treatment of stannane **4c**[20] (1.8 g, 4.0 mmol) in THF (5.5 mL) at 0°C with *n*-BuLi in hexanes (2.5 mL, 1.6 M). The suspension was stirred at -78°C for 1h, after which time a solution of **8** (0.73 g, 2.0 mmol) in Et_2O (10 mL) was added slowly *via* syringe. After stirring for 1 h, the temperature was slowly allowed to reach rt. The reaction mixture was poured into a saturated solution of $NaHCO_3$ (30 mL) and extracted with Et_2O (2x 60 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification of the crude product by silica gel column chromatography (elution: light petroleum/Et_3N, 99/1 → Et_2O/light petroleum/Et_3N, 25/75/1, v/v/v) afforded **11-*syn*** and **11-*anti*** as an inseparable mixture of diastereomers (ratio 5:2). Yield 0.20 g (19%). R_f 0.5 (Et_2O/light petroleum/Et_3N, 75/25/1). $^{13}C\{^1H\}$ NMR: δ 140.9, 139.2, 136.9 (Cq, arom), 133.4, 128.6-126.3 (CH, arom), 111.1 (Cq, isoprop), 104.7 (C-1), 84.7, 81.9, 81.3 (C-2, C-3, C-4), 71.4 (CH_2, OBn), 53.0 (C-5), 50.1 (CH_2, NBn), 26.6, 26.1 (CH_3, isoprop), 17.7 (C-6), -1.3, -1.9 ($SiCH_3$).

3-*O*-Benzyl-5-(*N*-benzyloxycarbonyl)benzylamino-5,6-dideoxy-6-dimethylphenylsilyl-1,2-*O*-isopropylidene-α-D-glucofuranose (14) - To a rapidly stirred solution of compound **11-*anti*** (0.53 g, 1.03 mmol) in 1,4-dioxane (4 mL) and H_2O (6 mL) was added $NaHCO_3$ (0.19 g, 2.58 mmol) and benzyl chloroformate (0.31 mL, 2.20 mmol). The reaction mixture was stirred for 1 h, concentrated to dryness and partitioned between Et_2O (30 mL) and H_2O (10 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (elution: Et_2O/light petroleum, 1/2 → 1/1, v/v) to give **14** as an oil. Yield 0.61 g (91%). R_f 0.7 (Et_2O/light petroleum, 3/1, v/v). MS (m/z): 652 $[M+H]^+$, 574 $[M+H-Ph]^+$, 518 $[M+H-Cbz]^+$. ^1H NMR (58°C): δ 7.43-7.16 (m, 20H, H-arom), 5.76 (d, 1H, H-1, $J_{1,2}$ 3.9 Hz), 5.05-5.00 (m, 3H, H-2, CH_2, Cbz), 4.51-4.20 (m, 4H, H-3, H-4, CH_2, OBn), 4.15 (AB, 2H, CH_2, NBn, *J* -15.4 Hz), 1.43, 1.20 (2x s, 6H, CH_3, isoprop), 1.29 (m, 1H, H-6a), 0.87 (dd, 1H, H-6b, $J_{5,6b}$ 5.1 Hz, $J_{6a,6b}$ -6.4 Hz), 0.20 (s, 6H, $SiCH_3$). $^{13}C\{^1H\}$ NMR (58°C): δ 157.4 (C=O), 139.4, 138.8, 137.4, 136.3 (Cq, arom), 133.3, 128.2-126.8 (CH, arom), 110.9 (Cq, isoprop), 104.3 (C-1), 82.1, 82.0, 81.6 (C-2, C-3, C-4), 71.4 (CH_2, OBn), 66.9, 66.7 (CH_2, Cbz, NBn), 52.9 (C-5), 26.4, 26.0 (CH_3, isoprop), -2.4, -2.9 ($SiCH_3$).

3-*O*-Benzyl-5-(*N*-benzyloxycarbonyl)benzylamino-5-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose (17) - AcOH (7.5 mL), NaOAc (1.0 g) and KBr (0.15 g, 1.2 mmol) were added to **14** (0.12 g, 1.12 mmol) and the mixture was stirred until the salts were dissolved. The solution was cooled (10°C) and AcOOH (5.0 mL, 30% in AcOH) was added dropwise under exclusion of light. During the addition gas was liberated. After the mixture was stirred for 3 h at 20°C, TLC analysis (Et_2O/light petroleum, 2/1, v/v) indicated complete conversion of the starting material into a more hydrophilic product (R_f 0.1). The mixture was diluted with Et_2O (30 mL) and poured into a cooled (0°C) solution of $Na_2S_2O_3$ (10 mL, 10%). The organic layer was washed with aqueous $NaHCO_3$ (10 mL) and treated with solid $NaHCO_3$ until no more gas evolved. The layers were separated and the organic layer was extracted with water (20 mL). The residue was dissolved in toluene (2x 4 mL) and concentrated before it was applied onto a column of silica gel, which was eluted with Et_2O/light petroleum (1/2 → 1/1, v/v). Concentration of the appropriate fractions gave **17** as an oil. Yield 0.35 g (70%). R_f 0.1 (Et_2O/light petroleum, 2/1, v/v). $[\alpha]_D^{20}$ -49.6 (c 2.0). MS (m/z): 534

$[M+H]^+$, 556 $[M+Na]^+$. ^1H NMR (58°C): δ 7.32-7.20 (m, 15H, H-arom), 5.85 (d, 1H, H-1, $J_{1,2}$ 4.9 Hz), 5.14 (AB, 2H, CH_2, Cbz, J -12.2 Hz), 4.79, 4.22 (AB, 2H, CH_2, NBn, J -15.8 Hz), 4.49 (AB, 2H, CH_2, Bn, J -11.6 Hz), 4.48 (d, 1H, H-2), 4.20 (m, 1H, H-5), 3.95-3.84 (m, 2H, H-3, H-4), 3.73 (m, 2H, H-6), 1.43, 1.34 (2x s, 6H, CH_3, isoprop). $^{13}C\{^1H\}$ NMR (58°C): δ 156.7 (C=O), 138.6, 137.1, 136.2 (Cq, arom), 128.2-127.0 (CH, arom), 111.5 (Cq, isoprop), 104.7 (C-1), 82.1, 81.3, 79.7 (C-2, C-3, C-4), 71.7, 67.3 (CH_2, Cbz, OBn), 62.9 (C-6), 57.6 (C-5), 50.6 (CH_2, NBn), 26.5, 26.1 (CH_3, isoprop).

5-Amino-5-deoxy-D-glucopyranose (1a) - Compound **17** (0.19 g, 0.36 mmol) was dissolved in MeOH (3.6 mL) in a 25 mL flask fitted with a septum. After a brief degassing at low vacuum, $Pd(OH)_2$ (18 mg, 10% on carbon) was added, the suspension degassed again, and a H_2-atmosphere was introduced. After 24 h, when TLC-analysis (EtOAc/MeOH, 7/3) indicated complete disappearance of UV-positive material, solids were filtered off (Hyflo), rinsed with MeOH, and solvent removed *in vacuo* to give crude 5-amino-5-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose. $[\alpha]_D^{20}$ -21.0 (c 1.0, CH_3OH). $^{13}C\{^1H\}$ NMR (CD_3OD): δ 113.1 (Cq, isoprop), 105.9 (C-1), 86.6, 77.6, 75.6 (C-2, C-3, C-4), 60.1 (C-6), 53.8 (C-5), 27.1, 26.4 (CH_3, isoprop). The crude oil was treated with SO_2 in H_2O (5 days) followed by basic hydrolysis of the resulting bisulfite adduct with Dowex 1-X8 (OH^-) according to reference 7b to give **1a** as white crystals. Yield 46 mg (71%). $[\alpha]_D^{20}$ +79.0 (c 0.2, H_2O)(Lit.[7b] 88). Mp 133-136°C (dec)(Lit.[23] 138-139°C).

1,5-Dideoxy-1,5-imino-D-glucitol (1b) - Compound **17** (0.16 g, 0.30 mmol) was dissolved in TFA/H_2O (9/1, v/v, 2 mL) and stirred for 1 h at rt. The mixture was diluted with toluene (10 mL) and evaporated with the same solvent (3x 2 mL). The residue was dissolved in MeOH (1 mL) and added to a suspension of $Pd(OH)_2$ on carbon (moisture ca. 50%) in H_2O/AcOH/MeOH (1/1/4, v/v/v, 4 mL). The mixture was shaken under a H_2-atmosphere (P_{H2} 0.5 MPa) for 48 h at ambient temperature, the catalyst was removed by filtration and the filtrate was treated with Amberlist IRA-400 [OH^-] (0.5 g). The ion-exchange resin was filtered off and the filtrate was concentrated *in vacuo*. The residual oil was applied onto a column of silica gel and elution effected with *n*-PrOH/H_2O/Et_3N (120/80/1, v/v/v) to give pure **1b** as a white solid. Yield 45 mg (84%). R_f 0.4 (*n*-PrOH/H_2O/Et_3N, 120/80/1, v/v/v). $[\alpha]_D^{20}$ +34.2 (c 0.1, H_2O). ^1H NMR (D_2O, pD 7.2): δ 3.80 (dd, 1H, H-6a, $J_{5,6a}$ 3.1 Hz, $J_{6a,6b}$ -11.7 Hz), 3.60 (dd, 1H, H-6b, $J_{5,6b}$ 6.3 Hz), 3.47 (ddd, 1H, H-2, $J_{1a,2}$ 5.1 Hz, $J_{1b,2}$ 10.7 Hz, $J_{2,3}$ 8.9 Hz), 3.29 (t, 1H, H-3, $J_{3,4}$ 9.0 Hz), 3.20 (t, 1H, H-4, $J_{4,5}$ 9.3 Hz), 3.08 (dd, 1H, H-1a, $J_{1a,1b}$ -12.3 Hz), 2.51 (ddd, 1H, H-5), 2.42 (dd, 1H, H-1b). $^{13}C\{^1H\}$ NMR (D_2O, pD 7.2): δ 79.1 (C-2), 72.1, 71.6 (C-3, C-4), 62.0 (C-6), 61.2 (C-5), 49.4 (C-1).

Methyl 5-*N*-benzylimino-5-deoxy-2,3-isopropylidene-α-D-lyxofuranoside (9) - Compound **6**[15] (2.34 g, 10.0 mmol) in MeOH was oxidatively cleaved with $NaIO_4$ and subsequently treated with $MgSO_4$ and $BnNH_2$ as described in the preparation of **8**, to give pure **9** after purification on silica gel. Yield 2.50 g (86%). ^1H NMR: δ 7.81 (t, 1H, H-5, $J_{4,5}$ 5.1 Hz, $J_{5,Bn}$ -1.5 Hz), 7.35-7.25 (m, 5H, H-arom), 5.00 (s, 1H, H-1), 4.90 (dd, 1H, H-3, $J_{2,3}$ 5.8 Hz, $J_{3,4}$ 3.9 Hz), 4.69 (AB, 2H, CH_2, Bn, J -12.6 Hz), 4.59 (d, 1H, H-2), 4.51 (dd, 1H, H-4), 3.34 (s, 3H, OCH_3), 1.47, 1.31 (2x s, 6H, CH_3, isoprop). $^{13}C\{^1H\}$ NMR: δ 161.6 (C-5), 138.2 (Cq, arom), 128.1, 127.8, 126.7 (CH, arom), 112.4 (Cq, isoprop), 107.3 (C-1), 84.7, 81.4, 80.5 (C-2, C-3, C-4), 64.6 (CH_2, Bn), 54.4 (OCH_3), 25.7, 24.4 (CH_3, isoprop).

Methyl 5-benzylamino-5,6-dideoxy-6-dimethylphenylsilyl-2,3-isopropylidene-α-D-mannofuranoside (12-*anti*) - Nucleophilic addition of the cuprate derived from **4b** in the presence

of $BF_3{\cdot}Et_2O$ to benzylimine **9** (0.58 g, 2.0 mmol) was executed as described above in the synthesis of **11**-*anti*, to give **12**-*anti* as an oil. Yield 0.67 g (76%). R_f 0.5 (EtOAc). $[\alpha]_D^{20}$ +26.2 (c 1.0). ^{1}H NMR (300 MHz): δ 7.57-7.16 (m, 10H, H-arom), 4.84 (s, 1H, H-1), 4.73 (dd, 1H, H-3, $J_{2,3}$ 5.9 Hz, $J_{3,4}$ 3.4 Hz), 4.51 (d, 1H, H-2), 3.80 (dd, 1H, H-4, $J_{4,5}$ 7.9 Hz), 3.76 (AB, 2H, CH_2, Bn, J -12.8 Hz), 3.28 (m, 1H, H-5), 3.26 (s, 3H, OCH_3), 1.39, 1.28 (2x s, 6H, CH_3, isoprop), 1.30 (dd, 1H, H-6a, $J_{5,6a}$ 4.8 Hz, $J_{6a,6b}$ -15.1 Hz), 1.13 (dd, 1H, H-6b, $J_{5,6b}$ 9.1 Hz), 0.34 (s, 6H, $SiCH_3$). $^{13}C\{^1H\}$ NMR: δ 140.8, 139.9 (Cq, arom), 133.4, 128.4-126.4 (CH, arom), 111.9 (Cq, isoprop), 106.4 (C-1), 85.0, 83.9, 79.7 (C-2, C-3, C-4), 54.1 (C-5), 52.9 (OCH_3), 50.7 (CH_2, Bn), 25.9, 24.7 (CH_3, isoprop), 19.4 (C-6), -2.0 ($SiCH_3$).

Methyl 5-benzylamino-5,6-dideoxy-6-dimethylphenylsilyl-2,3-isopropylidene-β-L-gulofuranoside (12-*syn*) -Nucleophilic addition of the organocerium reagent derived from **4d** to benzylimine **9** (0.79 g, 3.1 mmol) was executed as described above in the synthesis of **11**-*syn*, to give **12**-*syn* and **12**-*anti* as an intractable mixture (ratio 9:1). Yield 0.67 g (49%). R_f 0.5 (EtOAc). $^{13}C\{^1H\}$ NMR: δ 140.9, 138.2 (Cq, arom), 133.4, 128.7-127.6 (CH, arom), 112.2 (Cq, isoprop), 104.9 (C-1), 84.9, 84.7, 80.2 (C-2, C-3, C-4), 54.3 (OCH_3), 53.2 (C-5), 50.0 (CH_2, Bn), 25.9, 24.8 (CH_3, isoprop), 17.5 (C-6), -1.9, -2.0 ($SiCH_3$).

Methyl 5-(*N*-benzyloxycarbonyl)benzylamino-5,6-dideoxy-6-dimethylphenylsilyl-2,3-isopropylidene-α-D-mannofuranoside (15) - Compound **12**-*anti* (0.67 g, 1.5 mmol) was treated with benzyl chloroformate as described above for the synthesis of **14** to give **15**. Yield 0.69 g (79%). R_f 0.76 (Et_2O/light petroleum, 3/1, v/v). $[\alpha]_D^{20}$ +9.1 (c 2.0). ^{1}H NMR (58°C): δ 7.52-7.11 (m, 15H, H-arom), 5.08 (m, 2H, CH_2, Cbz), 4.86 (s, 1H, H-1), 4.77 (dd, 1H, H-3, $J_{2,3}$ 6.0 Hz, $J_{3,4}$ 3.4 Hz), 4.50 (d, 1H, H-2), 3.82-3.60 (m, 4H, H-4, H-5, CH_2, Bn), 3.30 (s, 3H, OCH_3), 1.37, 1.25 (2x s, 6H, CH_3, isoprop), 1.28-1.10 (m, 2H, H-6), 1.30, 1.28 (2x s, 6H, $SiCH_3$). $^{13}C\{^1H\}$ NMR (58°C): δ 157.3 (C=O), 140.2, 139.4, 136.8 (Cq, arom), 133.4, 128.4-127.3 (CH, arom), 111.9 (Cq, isoprop), 106.6 (C-1), 84.7, 79.6, 79.3 (C-2, C-3, C-4), 67.2, 66.7 (CH_2, Cbz, Bn), 54.2 (OCH_3), 25.8, 24.5 (CH_3, isoprop), 19.1 (C-6), -2.5 ($SiCH_3$).

Methyl 5-(*N*-benzyloxycarbonyl)benzylamino-5-deoxy-2,3-isopropylidene-α-D-mannofuranoside (18) - Compound **15** (0.69 g, 1.2 mmol) was oxidatively unmasked as described earlier for the conversion of **14**→**17**. After work-up and purification by silica gel column chromatography (elution: Et_2O/light petroleum, 1/3→1/1, v/v), alcohol **18** was obtained as an oil. Yield 0.42 g (76%). R_f 0.58 (Et_2O/light petroleum, 3/1, v/v). $[\alpha]_D^{20}$ +9.0 (c 1.0). ^{1}H NMR (58°C): δ 7.30-7.24 (m, 10H, H-arom), 5.17 (AB, 2H, CH_2, Bn, J -11.3 Hz), 4.83 (s, 1H, H-1), 4.62 (AB, 2H, CH_2, Bn, J -15.4 Hz), 4.57-4.40 (m, 2H, H-2, H-3), 3.93-3.65 (m, 4H, H-4, H-5, H-6), 3.24 (s, 3H, OCH_3), 1.45, 1.28 (CH_3, isoprop). $^{13}C\{^1H\}$ NMR (58°C): δ 156.8 (C=O), 138.6, 136.5 (Cq, arom), 128.4-127.3 (CH, arom), 112.3 (Cq, isoprop), 107.2 (C-1), 84.8, 79.9, 78.4 (C-2, C-3, C-4), 67.4 (CH_2, Cbz), 63.1 (C-6), 60.0 (C-5), 54.2 (OCH_3), 52.8 (CH_2, Bn), 26.0, 24.8 (CH_3, isoprop).

Methyl 5-amino-5-deoxy-2,3-isopropylidene-α-D-mannofuranoside - Hydrogenation of compound **18** (0.11 g, 0.25 mmol) was performed as for the debenzylation of **17** to give the title compound after silica gel column chromatography (elution: EtOAc/Et_3N, 98/2, v/v). Yield 70 mg (100%). $[\alpha]_D^{20}$ +64.7 (c 2.0). ^{1}H NMR: δ 4.88 (s, 1H, H-1), 4.78 (dd, 1H, H-3, $J_{2,3}$ 6.0 Hz, $J_{3,4}$ 3.6 Hz), 4.55 (d, 1H, H-2), 3.81 (dd, 1H, H-6a, $J_{5,6a}$ 7.0 Hz, $J_{6a,6b}$ -10.7 Hz), 3.78 (dd, 1H, H-4, $J_{4,5}$ 8.9 Hz), 3.59 (dd, 1H, H-6b, $J_{5,6b}$ 6.5 Hz), 3.30 (s, 3H, OCH_3), 3.21 (m, 1H, H-5), 2.43 (bs, 3H, NH_2, OH), 1.45, 1.32 (2x s, 6H, CH_3, isoprop). $^{13}C\{^1H\}$ NMR: δ 112.2 (Cq, isoprop), 106.8 (C-1), 84.5,

79.9, 79.6 (C-2, C-3, C-4), 63.3 (C-6), 54.1 (OCH_3), 51.9 (C-5), 25.7, 24.5 (CH_3, isoprop). Conversion into 5-amino-5-deoxy-D-mannopyranose (**2a**) was not further investigated.

1,5-Dideoxy-1,5-imino-D-mannitol (2b) - Compound **18** (0.35 g, 0.77 mmol) was dissolved in 80% aqueous AcOH and heated until reflux. After 6 h, the mixture was concentrated under reduced pressure and the residual oil coevaporated with toluene (3x 2 mL). The residue was dissolved in MeOH and hydrogenenated as described in the synthesis of **1b**, to give pure **2b** after silica gel column chromatography. Yield 0.12 g (86%). R_f 0.3 (*n*-PrOH/H_2O/MeOH, 120/80/1, v/v/v). $[\alpha]_D^{20}$ -37.3 (c 0.4, H_2O)(Lit.[10b] -40). ^1H NMR (D_2O, pD 7.2): δ 4.09 (dt, 1H, H-2, $J_{1a,2}$ $J_{1b,2}$ 1.4 Hz, $J_{2,3}$ 3.2 Hz), 3.86 (dd, 1H, H-6a, $J_{5,6a}$ 3.1 Hz, $J_{6a,6b}$ -11.9 Hz), 3.78 (dd, 1H, H-6b, $J_{5,6b}$ 5.3 Hz), 3.71 (t, 1H, H-4, $J_{3,4}$ $J_{4,5}$ 9.7 Hz), 3.61 (dd, 1H, H-3), 3.12 (dd, 1H, H-1a, $J_{1a,1b}$ -14.0 Hz), 2.95 (dd, 1H, H-1b), 2.74 (ddd, 1H, H-5). $^{13}C\{^1H\}$ NMR (D_2O): δ 76.3, 70.5, 69.9 (C-2, C-3, C-4), 63.0 (C-5), 62.8 (C-6), 50.5 (C-1).

Methyl 2,3-di-*O*-benzyl-5-benzylimino-5-deoxy-α-L-arabinofuranoside (10) - Compound 7[16] (3.12 g, 8.31 mmol) in MeOH was oxidatively cleaved with $NaIO_4$ and subsequently treated with $MgSO_4$ and $BnNH_2$ as described in the preparation of **8**, to give pure **10** after purification on silica gel. Yield 2.40 g (67%). R_f 0.7 (toluene/EtOAc, 5/1, v/v). ^1H NMR: δ 7.74 (d, 1H, H-5, $J_{4,5}$ 4.9 Hz), 7.34-7.25 (m, 15H, H-arom), 4.99 (s, 1H, H-1), 4.62 (AB, 2H, CH_2, Bn, *J* -11.6 Hz), 4.56 (AB, 2H, CH_2, Bn, *J* -12.2 Hz), 4.46 (s, 2H, CH_2, Bn), 4.05-4.01 (m, H-2, H-3, H-4), 3.40 (s, 3H, OCH_3). $^{13}C\{^1H\}$ NMR: δ 162.9 (C-5), 138.2, 137.2, 137.0 (Cq, arom), 128.2-126.7 (CH, arom), 107.2 (C-1), 87.5, 84.5, 83.0 (C-2, C-3, C-4), 71.5, 71.4 (CH_2, OBn), 64.2 (CH_2, NBn), 54.6 (OCH_3).

Methyl 2,3-di-*O*-benzyl-5-benzylamino-5,6-dideoxy-6-dimethylphenylsilyl-α-L-altrofuranoside (13-*anti*) -Nucleophilic addition of the cuprate derived from **4b** in the presence of $BF_3{\cdot}Et_2O$ to benzylimine **10** (0.86 g, 2.0 mmol) was executed as described above in the synthesis of **11**-*anti*, to give **13**-*anti* and **13**-*syn* as a mixture of diastereoisomers (ratio 5:2). Yield 0.85 g (73%). R_f 0.5-0.8 (Et_2O/light petroleum, 1/1, v/v). $^{13}C\{^1H\}$ NMR, **13**-*anti*: δ 140.5, 139.4, 137.6, 137.4 (Cq, arom), 133.3, 128.5-127.5 (CH, arom), 106.8 (C-1), 87.7, 83.8, 83.2 (C-2, C-3, C-4), 54.8 (C-5), 54.4 (OCH_3), 51.2 (CH_2, Bn), 17.1 (C-6), -2.2, -2.3 ($SiCH_3$).

Methyl 2,3-di-*O*-benzyl-5-benzylamino-5,6-dideoxy-6-dimethylphenylsilyl-β-D-galactofuranoside (13-*syn*) - Nucleophilic addition of the organocerium reagent derived from **4d** to benzylimine **10** (0.75 g, 1.73 mmol) was executed as described above in the synthesis of **11**-*syn*, to give **13**-*syn* as an oil. Yield 0.57 g (57%). R_f 0.6-0.8 (Et_2O/light petroleum, 1/1, v/v). $[\alpha]_D^{20}$ -56.8 (c 0.5). ^1H NMR (300 MHz): δ 7.51-7.12 (m, 20H, H-arom), 4.89 (s, 1H, H-1), 4.49 (AB, 2H, CH_2, OBn, *J* -11.9 Hz), 4.39 (AB, 2H, CH_2, OBn, *J* -12.0 Hz), 4.09 (dd, 1H, H-3, *J* 4.7 Hz, *J* 5.9 Hz), 3.96-3.93 (m, 2H, H-2, H-4), 3.67 (AB, 2H, CH_2, NBn, *J* -12.7 Hz), 3.34 (s, 3H, OCH_3), 2.86 (dt, 1H, H-5, $J_{4,5}$ $J_{5,6a}$ 6.8 Hz, $J_{5,6b}$ 4.5 Hz), 1.22 (dd, 1H, H-6a, $J_{6a,6b}$ -7.4 Hz), 1.06 (dd, 1H, H-6b), 0.30, 0.29 (2x s, 6H, $SiCH_3$). $^{13}C\{^1H\}$ NMR: δ 140.5, 139.1, 137.6, 137.4 (Cq, arom), 133.3, 128.5-126.3 (CH, arom), 106.7 (C-1), 88.1, 83.9, 83.1 (C-2, C-3, C-4), 71.5, 71.4 (CH_2, OBn), 54.4, 54.3 (C-5, OCH_3), 50.5 (CH_2, NBn), 17.2 (C-6), -2.1, -2.4 ($SiCH_3$).

Methyl 2,3-di-*O*-benzyl-5-(*N*-benzyloxycarbonyl)benzylamino-5,6-dideoxy-6-dimethylphenylsilyl-β-D-galactofuranoside (16) - Compound **13**-*syn* (0.57 g, 0.28 mmol) was treated with benzyl chloroformate as described above for the synthesis of **14** to give **16**. Yield 0.60 g (85%). R_f 0.6 (toluene/EtOAc, 5/1, v/v). $[\alpha]_D^{20}$ -29.3 (c 2.0). ^1H NMR (58°C): δ 7.59-7.20 (m,

25H, H-arom), 5.05 (s, 1H, H-1), 4.53-4.26 (m, 6H, CH_2, OBn, Cbz), 4.00 (t, 1H, H-3, $J_{2,3}$ $J_{3,4}$ 5.0 Hz), 3.87-3.83 (m, 2H, H-2, H-4), 3.76-3.60 (m, 3H, H-5, CH_2, NBn), 3.16 (s, 3H, OCH_3), 1.30-1.11 (m, 2H, H-6), 0.21 (bs, 6H, $SiCH_3$). $^{13}C\{^1H\}$ NMR (58°C): δ 156.8 (C=O), 140.1, 139.2, 137.8, 137.5 (Cq, arom), 133.3, 128.7-126.2 (CH, arom), 106.7 (C-1), 88.1, 84.9, 83.8 (C-2, C-3, C-4), 71.9, 71.5 (CH_2, OBn), 66.9 (CH_2, Cbz, NBn), 54.7, 54.4 (C-5, OCH_3), 16.8 (C-6), -2.9 ($SiCH_3$).

Methyl 2,3-di-*O*-benzyl-5-(*N*-benzyloxycarbonyl)benzylamino-5-deoxy-β-D-galactofuranoside (19) - Compound **16** (0.60 g, 0.84 mmol) was oxidatively unmasked as described earlier for the conversion of **14**→**17**. After work-up and purification by silica gel column chromatography (elution: Et_2O/light petroleum, 1/3→1/1, v/v), alcohol **19** was obtained as an oil. Yield 0.33 g (66%). R_f 0.3 (Et_2O/light petroleum, 3/1, v/v). $[\alpha]_D^{20}$ -26.2 (c 2). $^{13}C\{^1H\}$ NMR (58°C): δ 157.3 (C=O), 139.1, 137.2 (Cq, arom), 127.9-126.8 (CH, arom), 106.8 (C-1), 88.2, 85.1, 79.7 (C-2, C-3, C-4), 67.3 (CH_2, Cbz), 62.1 (C-6), 61.3 (C-5), 54.5 (OCH_3), 49.9 (CH_2, Bn).

Methyl 5-amino-5-deoxy-β-D-galactofuranoside - Hydrogenation of compound **19** (0.15 g, 0.25 mmol) was performed as for the debenzylation of **17** to give the title compound after silica gel column chromatography (elution: EtOAc/MeOH, 9/1, v/v). Yield 45 mg (98%). $^{13}C\{^1H\}$ NMR (CD_3OD): δ 110.8 (C-1), 82.7, 82.6, 80.3 (C-2, C-3, C-4), 60.8 (C-6), 56.6 (C-5), 55.4 (OCH_3). Conversion into 5-amino-5-deoxy-D-galactopyranose (**3a**) was not further investigated.

1,5-Dideoxy-1,5-imino-D-galactitol (3b) - Compound **19** (0.20 g, 0.44 mmol) was treated with 80% aqueous AcOH under reflux (48 h) as described in the synthesis of **2b**. The residue was dissolved in MeOH and hydrogenenated as described in the synthesis of **1b**, to give pure **3b** after silica gel column chromatography. Yield 51 mg (65%). R_f 0.2 (*n*-PrOH/H_2O/MeOH, 120/80/1, v/v/v). $[\alpha]_D^{20}$ +50.3 (c 0.2, H_2O)(Lit.[9d] +52.8). ^1H NMR (D_2O, pD 7.2): δ 4.18 (dd, 1H, H-4, $J_{3,4}$ 3.1 Hz, $J_{4,5}$ 1.3 Hz), 3.93 (ddd, 1H, H-2, $J_{1a,2}$ 10.8 Hz, $J_{1b,2}$ 5.3 Hz, $J_{2,3}$ 9.7 Hz), 3.83 (dd, 1H, H-6a, $J_{5,6a}$ 6.6 Hz, $J_{6a,6b}$ -10.8 Hz), 3.78 (dd, 1H, H-6b, $J_{5,6b}$ 6.6 Hz), 3.65 (dd, 1H, H-3), 3.31 (dd, 1H, H-1a, $J_{1a,1b}$ -12.6 Hz), 2.92 (dt, 1H, H-5), 2.56 (dd, 1H, H-1b). $^{13}C\{^1H\}$ NMR (MeOD): δ 77.1, 70.7, 69.3 (C-2, C-3, C-4), 62.9 (C-6), 61.9 (C-5), 50.7 (C-1).

References and notes

1. van Delft, F.L.; Krempel, R.N.T.C.; de Kort, M.; van der Marel, G.A.; van Boom, J.H. *manuscript in preparation.*
2. (a) Legler, G. *Adv. Chem. Biochem.* **1990**, *48*, 318. (b) Winchester, B.; Fleet, G.W.J. *Glycobiology* **1992**, *2*, 199. (c) van den Broek, L.A.G.M.; Vermaas, D.J.; van Kemenade, F.J.; Tan, M.C.C.A.; Rotteveel, F.T.M.; Zandberg, P.; Butters, T.D.; Miedema, F.; Ploegh, H.L.; van Boeckel, C.A.A. *Recl. Trav. Chim. Pays-Bas* **1994**, *113*, 507. (d) Asano, N.; Kizu, H.; Oseki, K.; Tomioka, E.; Matsui, K.; Okamoto, M.; Baba, M. *J. Med. Chem.* **1995**, *38*, 2349.
3. Paulsen, H. *Justus Liebigs Ann. Chem.* **1965**, *683*, 187.
4. (a) Horii, S.; Fukase, H.; Matsuo, T.; Kameda, Y.; Asano, N.; Matsui, K. *J. Med. Chem.* **1986**, *29*, 1038. (b) Anzenevo, P.B.; Creemer, L.J.; Daniel, J.K.; King, C.-H.R.; Liu, O.S. *J. Org. Chem.* **1989**, *54*, 2539.

5. (a) Dennis, J.W. *Cancer Res.* **1986**, *46*, 5131. (b) Humphries, K.J.; Matsumoto, K.; White, S.; Olden, K. *ibid.* **1986**, *46*, 5215.
6. (a) Platt, F.M.; Neises, G.R.; Dwek, R.A.; Butters, T.D. *J. Biol. Chem.* **1994**, *269*, 8362. (b) Block, T.M.; Lu, X.; Platt, F.M.; Foster, G.R.; Gerlich, W.H.; Blumberg, B.S.; Dwek, R.A. *Proc. Natl. Acad. Sci. USA* **1994**, *91*, 2235.
7. (1-Deoxy)nojirimycin: (a) Ishida, N.; Kumagai, K.; Niida, T.; Tsuruoka, T.; Yumato, H. *J. Antibiot.* **1967**, *20*, 66. (b) Inouye, S.; Tsuruoka, T.; Ito, T.; Niida, T. *Tetrahedron* **1968**, *23*, 2125. (c) Hughes, A.B.; Rudge, A.J. *Nat. Prod. Reports* **1994**, *11*, 135.
8. (1-Deoxy)mannojirimycin: (a) Fellows, L.E.; Bell, E.A.; Lynn, D.G.; Pilkiewicz, F.; Miura, I.; Nakanishi, K. *J. Chem. Soc., Chem. Commun.* **1979**, 977. (b) Niwa, T.; Tsuruoka, T.; Goi, H.; Itoh, J.; Inoue, S.; Yamada, Y.; Niida, T.; Nobe, M.; Ogawa, Y. *J. Antibiot.* **1984**, *37*, 1579. (c) Bischoff, J.; Kornfeld, R. *J. Biol. Chem.* **1983**, *258*, 7907. (d) Legler, G.; Jülich, E. *Carbohydr. Res.* **1984**, *128*, 61. (e) Slusarewicz, P.; Warren, G. *Glycobiology* **1995**, *5*, 154.
9. (1-Deoxy)galactostatin: (a) Paulsen, H.; Hayauchi, Y.; Sinnwell, V. *Chem. Ber.* **1980**, *113*, 2601. (b) Legler, G.; Pohl, S. *Carbohydr. Res.* **1986**, *155*, 119. (c) Bernotas, R.C.; Pezzone, M.A.; Ganem, B. *Carbohydr. Res.* **1987**, *167*, 305. (d) Miyake, Y.; Ebata, M. *Agric. Biol. Chem.* **1988**, *52*, 661.
10. (a) Broxterman, H.J.G.; van der Marel, G.A.; Neefjes, J.J.; Ploegh, H.L.; van Boom, J.H. *Recl. Trav. Chim. Pays-Bas* **1987**, *106*, 571. (b) Broxterman, H.J.G.; van der Marel, G.A.; Neefjes, J.J.; Ploegh, H.L.; van Boom, J.H. *J. Carbohydr. Chem.* **1988**, *7*, 593.
11. van der Klein, P.A.M.; Filemon, W.; Broxterman, H.J.G.; van der Marel, G.A.; van Boom, J.H. *Synth. Commun.* **1992**, *22*, 1763.
12. Smid, P.; Schipper, F.J.M.; Broxterman, H.J.G.; van der Marel, G.A.; van Boom, J.H. *Recl. Trav. Chim. Pays-Bas* **1993**, *112*, 451.
13. van Delft, F.L.; de Kort, M.; van der Marel, G.A.; van Boom, J.H. *Tetrahedron: Asymmetry* **1994**, *5*, 2261.
14. Fleet, G.W.J.; Witty, D.R. *Tetrahedon: Asymmetry* **1990**, *1*, 119.
15. Evans, M.E.; Parrish, F.W. *Methods Carbohydr. Chem.* **1980**, *8*, 173.
16. Rao, A.S.; Roy, N. *Carbohydr. Res.* **1977**, *59*, 393.
17. McCarty, C.G. in *The Chemistry of the Carbon-Nitrogen Double Bond*, Patai, S., Ed.; Interscience: London, 1970; pp 363.
18. Wada, M.; Sakurai, Y.; Akiba, K. *Tetrahedron Lett.* **1984**, *25*, 1079.
19. Seitz, D.E.; Zapata, A. *Synthesis* **1981**, 557.
20. (a) Chapter V. (b) van Delft, F.L.; de Kort, M.; van der Marel, G.A.; van Boom, J.H. *Carbohydr. Lett.* **1996**, *in press.*
21. Imamoto, T. in *Comprehensive Organic Synthesis* Trost, B.M., Fleming, I., Eds.; Pergamon Press, Oxford, 1991, Vol 3, pp 231.
22. (a) Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392. (b) Bartoli, G.; Marcantoni, E.; Petrini, M.; Ogata, K. *Tetrahedron Lett.* **1991**, *32*, 2787.
23. Tsuda, Y.; Okuno, Y.; Kanemitsu, K. *Heterocycles* **1988**, *27*, 63.

V

Hydroxymethylation of Carbohydrate Imines: Formal Synthesis of the 4-Ethylamino Sugar of Calicheamicin[1]

Abstract

The 4-ethylamino sugar **12** of calicheamicin γ_1^I is prepared from D-glucose *via* highly diastereoselective hydroxymethylation of the readily available ethylimino sugar **4**.

Introduction

Calicheamicin γ_1^I (Figure 1) is an important member[2] of the enediyne class of naturally occurring antitumor antibiotics termed enediynes[3]. These novel compounds contain conjugated unsaturated systems as a common structural feature and have attracted considerable attention owing to their potent biological activity and novel mechanism of action as double strand DNA cleaving agents.

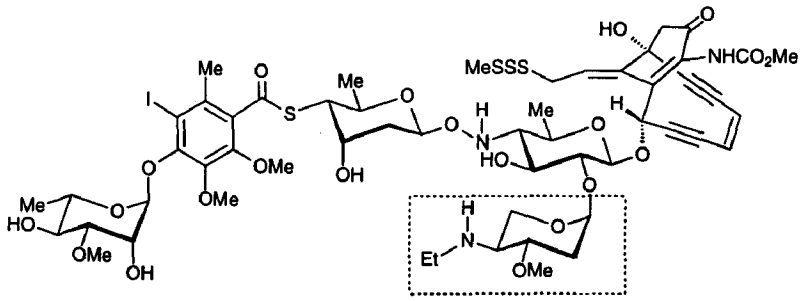


Figure 1. Structure of the enediyne antibiotic calicheamicin γ_1^I.

Enediyne antibiotics can be viewed as a natural kind of prodrugs[4] because they have to undergo an activation step before they unfold biological activity. In order to do this, the enediyne antibiotics are equipped with three important functional domains: (a) a *delivery system* (*i.e.* the carbohydrate component) responsible for targeting DNA, (b) a *warhead* (*i.e.* the enediyne part) that "explodes" upon activation, thus providing the fragments that damage DNA and (c) a *triggering device* (*i.e.* the trisulfide unit), which after activation, initiates a cascade of reactions leading eventually to the generation of aromatic diradicals from the warhead. The trigger mechanism is an essential feature for controlling and minimizing side effects during distribution in the body[3].

The unusual oligosaccharide part of the antibiotic accounts for the highly site selective binding into the DNA minor groove with specificity for oligopyrimidine-oligopurine runs[5]. In this respect, NMR studies indicated that the DNA-embedded conformation of calicheamicin is very similar to the average solution conformation, primarily so due to the presence of the unusual N-O glycosidic linkage[6]. In order to understand in more detail the nature of the DNA-oligosaccharide interaction, several laboratories have focussed on the synthetic assembly of calicheamicin and at present two total syntheses have been completed[7].

Earlier results from our laboratory[8] have shown that the Grignard reagent **1b** (Scheme 1), derived from commercially available (chloromethyl)dimethylphenyl silane (**1a**), is a useful reagent for hydroxymethylation of carbohydrate aldehydes and hemiacetals. Apart from this, we reported[9] that reagent **1b** can be applied for the preparation of vicinal amino alcohols *via* nucleophilic chain-extension of imines. For example, the cerium(III)- or copper(I)-mediated addition of **1b** to 6-benzylimino-6-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose proceeded with excellent diastereoselectivity to the respective *syn*- and *anti*-adducts, which were further processed into known precursors of the antibiotics destomic acid and lincomycin (Chapter III).

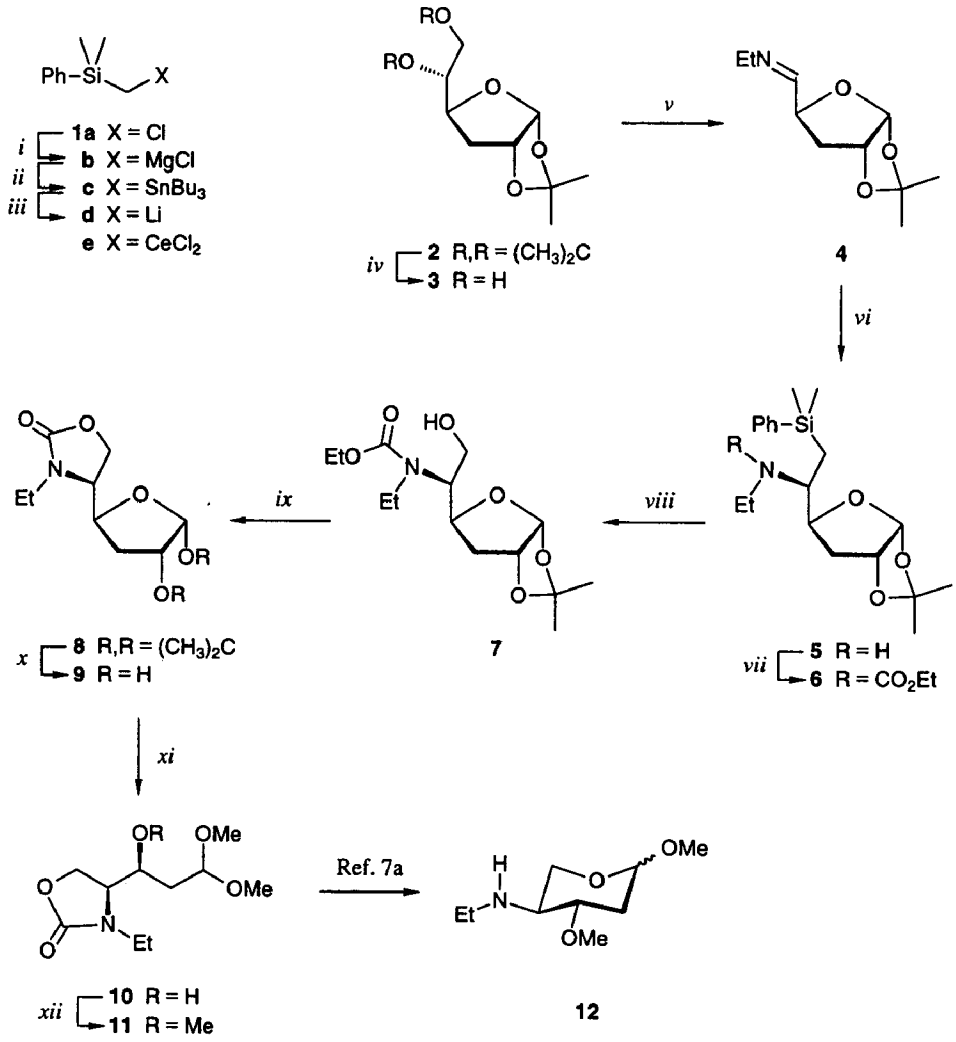
We now wish to report the stereoselective synthesis of 2-oxazolidinone **11**, a known[7a,10] precursor of 4-ethylamino sugar **12**[11], *via* cerium-mediated nucleophilic addition of the organolithium reagent **1d** to 3,5-dideoxy-5-ethylimino-1,2-*O*-isopropylidene-α-D-*erythro*-pentofuranose (**4**).

Results and discussion

The construction of the target 2-oxazolidinone **11** starts with 3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranose (**2**), readily obtained in 85% yield by deoxygenation[12] of commercially available 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose. Regioselective deacetonation of the 5,6-isopropylidene function in **2** is effected with aqueous acetic acid to give diol **3** in 92% yield after purification. Sodium periodate cleavage of the diol function and treatment of the resulting aldehyde with excess

ethylamine hydrochloride - triethylamine led to the isolation of isomerically pure[13] ethylimino sugar **4**. From previous results it was anticipated[9] that nucleophilic addition of Grignard reagent **1b**, precomplexed with $CeCl_3$, would lead to the formation of the

Scheme 1



Reagents and conditions

(*i*) Mg, THF, reflux, 2 h; (*ii*) Bu_3SnCl, THF, 0°C, 16 h (91% from **1a**); (*iii*) *n*-BuLi, THF, 0°C, 0.5 h; (*iv*) 80% AcOH, 16 h (92%); (*v*) (a) $NaIO_4$, MeOH, 2 h (b) $EtNH_2.HCl$, Et_3N, $MgSO_4$, $PhCH_3$, 8 h (83%); (*vi*) **1d**, $CeCl_3$, THF/Et_2O, -78°C → 0°C (49%); (*vii*) $ClCO_2Et$, $NaHCO_3$, 1,4-dioxane, H_2O, 1 h (88%) or $ClCO_2Et$, 20 min (81% from **4**); (*viii*) KBr, AcO_2H, NaOAc, AcOH, 2.5 h (77%); (*ix*) THF, NaH, 1 h (93%); (*x*) 60% TFA, 10 min (91%); (*xi*) (a) $NaIO_4$, MeOH, 3 h (b) Dowex-H^+, MeOH, 20 h (88%); (*xii*) Ag_2O, MeI, DMF, 40°C, 16 h (89%).

requisite *syn*-diastereomeric β-aminosilane adduct. Unfortunately, ^{1}H NMR analysis of the reaction mixture revealed the sole presence of starting imine **4** and no trace of addition products. The disappointing outcome of the addition may be ascribed[14] to the fact that the efficacy of the organocerium reagent **1e** is diminished by the *in situ* generated $MgCl_2$. In order to eliminate this possibility, reagent **1e** was prepared by complexation of the organolithium reagent **1d** with cerium(III) chloride. Thus, stannylation of **1b** with tri-*n*-butyltin chloride gave, after distillation, the stannane derivative **1c**. Transmetallation[15] of **1c** with *n*-butyllithium in THF at 0°C gave **1d** in a quantitative yield. Imine **4** was now added dropwise to **1e** formed *in situ* from **1d** and cerium(III) chloride in diethyl ether. ^{1}H NMR spectroscopy of the resulting crude aminosilane adduct **5** revealed the presence of one diastereoisomer. Reaction of purified **5** with ethyl chloroformate, under Schotten-Baumann conditions, gave the urethane **6** in a yield of 43% for the two steps. Alternatively, a two-fold increase in yield of **6** was attained by adding ethyl chloroformate[16] to the *in situ* formed addition product of **4** with **1e**. Oxidative unmasking of the silyl moiety was performed under standard Fleming conditions, *i.e.* treatment of **6** with potassium bromide and peracetic acid in buffered acetic acid[17]. The resulting alcohol **7** was cyclized with sodium hydride in THF to give crystalline 2-oxazolidinone **8**. The absolute configuration of the newly introduced stereocenter at C-5 in **8** was irrefutably established by X-ray analysis[18] (Figure 2), thus confirming the *syn*-stereoselectivity of the nucleophilic addition of organocerium reagent **1e** to imine **4**.

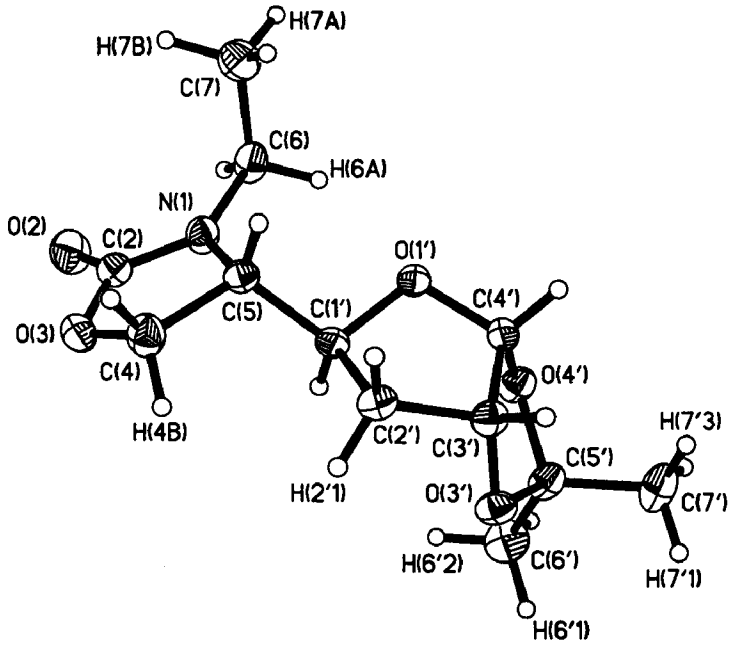


Figure 2. ORTEP diagram of 2-oxazolidinone **8** showing crystallographic numbering[18].

The 1,2-isopropylidene function in **8** was removed with aqueous trifluoroacetic acid to give diol **9** as a mixture of anomers ($\alpha/\beta \approx 4/1$). Oxidative cleavage of **9** with sodium periodate, followed by acetalization of the resulting aldehyde with Dowex-H^+ in dry methanol, led to the isolation of **10**. Methylation of **10** with iodomethane in the presence of silver(I) oxide gave the 2-oxazolidinone **11** (32% overall yield, based on **2**), which can be readily transformed into 4-ethylamino sugar **12** by a two-step procedure reported[7a,10] by Nicolaou *et al.*

Conclusion

A stereoselective approach towards the synthesis of a precursor of the novel 4-ethylamino sugar (**12**)[11] of calicheamicin has been described, which compares well with previously reported[10,19] routes to **12** in terms of stereoselectivity, number of steps and costs. At present we are in the process of using this new methodology for the construction of other naturally occurring rare aminosugars.

Acknowledgement We are indebted to professor A.H.-J. Wang of the University of Illinois at Urbana-Champaign for executing the X-ray analysis.

Experimental

General methods and materials - Toluene was distilled from P_2O_5 and stored over 4Å molecular sieves, tetrahydrofuran and Et_2O were freshly distilled from $LiAlH_4$ and dried over 4Å molecular sieves for two hours. *N,N*-Dimethylformamide was distilled from CaH_2 and stored on 3Å molecular sieves. Triethylamine was distilled from CaH_2. Methanol (HPLC-grade, Rathburn), 1,4-dioxane and acetic acid were used as received. All reactions were performed under strictly anhydrous conditions unless noted otherwise. Concentration was carried out below 40°C under reduced pressure. Reactions were followed by TLC analysis on Schleicher and Schüll DC Fertigfolien F 1500 LS 254. Compounds were visualized by UV light (254 nm) followed by spraying with 20% sulfuric acid in methanol and charring at 140°C. Column chromatography was performed on silica gel 60, 230-400 mesh (Merck). Unless noted otherwise, ^1H and ^{13}C NMR spectra were recorded in deuterated chloroform at rt with a Jeol JNM-FX200 spectrometer at 200 and 50.1 MHz, respectively or a Bruker 600-DMX spectrometer (600 MHz ^1H NMR spectroscopy). Chemical shifts (δ) are reported in ppm relative to tetramethylsilane as internal standard. Optical rotations were measured in chloroform on a Propol automatic polarimeter. Mass spectra (FAB) were recorded on a Finnigan MAT TSQ70 triple quadrupole mass spectrometer.

[(Phenyldimethylsilyl)methyl] tri-*n*-butylstannane (1c) - A small amount (0.5 mL) of (chloromethyl)dimethylphenylsilane (9.02 mL, 50 mmol) in THF (50 mL) was added under a N_2-atmosphere to dry magnesium powder (1.34 g, 55 mmol) and the reaction mixture was heated until reflux. The reaction was initiated by the addition of 1,2-dibromoethane (0.1 mL) and the remaining chloride was added at such a rate as to maintain a gentle reflux. After stirring the thus

obtained metallic solution at 40°C for an additional hour it was cooled to 0°C, a solution of tri-*n*-butyltin chloride (14.9 mL, 55 mmol) in THF (50 mL) was added dropwise and stirring continued for 16 h. The mixture was slowly poured into aqueous ammonium chloride (50 mL, 20%) and extracted with Et_2O (200 mL). The organic layer was washed with H_2O (50 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The liquid thus obtained was purified by vacuum distillation to give **1c**. Yield 20.0 g (91%). Bp 143-146°C (0.3 mmHg). ^1H NMR: δ 7.55-7.50 (m, 2H, H-arom), 7.36-7.26 (m, 3H, H-arom), 1.53-1.21 (m, 12H, 6x CH_2, Bu), 0.88 (t, 12H, 3x CH_3, Bu), 0.80 (t, 6H, 3x $SnCH_2$, Bu), 0.28 (s, 6H, $SiCH_3$), -0.05 (s, 2H, $SiCH_2Sn$). $^{13}C\{^1H\}$ NMR: δ 140.8 (Cq, arom), 133.2, 128.6, 127.7 (CH, arom), 29.1, 27.4 (CH_2, Bu), 13.7 (CH_3, Bu), 10.3 ($SiCH_2$, Bu), 0.3 ($SiCH_3$), -8.6 ($SiCH_2Sn$).

3,5-Dideoxy-5-ethylimino-1,2-*O*-isopropylidene-α-D-*erythro*-pentofuranose (4) - To a rapidly stirred solution of diol **3**[20] (1.36 g, 6.7 mmol) in methanol (60 mL), a solution of $NaIO_4$ (1.75 g, 8.0 mmol) in H_2O (4 mL) was added. The resulting turbid solution was stirred for 2 h, after which time TLC analysis indicated complete disappearance of starting material. The mixture was filtered, concentrated, taken up in Et_2O (100 mL) and washed with H_2O (2x 10 mL). The aqueous phases were combined and extracted with Et_2O (50 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The oily product was dissolved in toluene (35 mL) and cooled (0°C), before $MgSO_4$ (1.60 g, 13.3 mmol), Et_3N (1.84 mL, 13.3 mmol) and ethylamine hydrochloride (0.82 g, 10.0 mmol) were added. The mixture was stirred overnight at 0°C, filtered and concentrated. Flash chromatography over silica gel (Et_2O/light petroleum/Et_3N, 50/50/1, v/v/v) gave **4** as a colorless oil. Yield 1.10 g (83%). R_f 0.3 (Et_2O). $^{13}C\{^1H\}$ NMR: δ 162.4 (C-5), 110.9 (Cq, isoprop), 105.7 (C-1), 80.4, 78.8 (C-2, C-4), 54.3 (CH_2, Et), 36.3 (C-3), 26.4, 25.8 (CH_3, isoprop), 15.4 (CH_3, Et).

5-Amino-6-dimethylphenylsilyl-5-*N*-ethyl-3,5,6-trideoxy-1,2-*O*-isopropylidene-β-L-*lyxo*-hexofuranose (5) - Under high vacuum (1 mmHg), $CeCl_3.7H_2O$ (4.66 g, 12.5 mmol) was dried at 140°C for 2 h. After cooling to rt, Et_2O (50 mL) was added and the resulting suspension was stirred overnight. The mixture was cooled (-78°C) and a solution of **1d** in THF (15 mL), prepared by treatment of **1c** (5.71 g, 13 mmol) at 0°C with *n*-BuLi (8.13 mL, 1.6 M in hexane) for 30 min[15], was added slowly. After stirring for 1 h at -78°C, a solution of freshly prepared **4** (1.10 g, 5.5 mmol) in THF (10 mL) was added dropwise. The mixture was kept at -78°C for another hour and the temperature was allowed to raise slowly to 0°C. The mixture was poured, with vigorous stirring, into a saturated solution of NaCl (50 mL), the layers were separated and the organic phase washed with H_2O (50 mL). The combined aqueous layers were extracted with Et_2O (2x 50 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Silica gel column chromatography (Et_2O) of the residual oil afforded pure **5**. Yield 0.95 g (49%). $[\alpha]_D^{20}$ -0.7 (c 0.8). R_f 0.1-0.2 (Et_2O). MS (m/z): 350 $[M+H]^+$. ^1H NMR: δ 7.55-7.49 (m, 2H, H-arom), 7.35-7.25 (m, 3H, H-arom), 5.73 (d, 1H, H-1, $J_{1,2}$ 3.9 Hz), 4.64 (t, 1H, H-2, $J_{2,3a}$ 4.7 Hz), 4.19 (ddd, 1H, H-4, $J_{3a,4}$ 10.7 Hz, $J_{3b,4}$ 4.3 Hz, $J_{4,5}$ 5.8 Hz), 2.75 (dt, 1H, H-5, $J_{5,6a}$ 5.8 Hz, $J_{5,6b}$ 7.5 Hz), 2.53 (q, 2H, CH_2, Et, J 7.1 Hz), 1.92 (dd, 1H, H-3b, $J_{3a,3b}$ -13.3 Hz), 1.64 (ddd, 1H, H-3a), 1.46, 1.29 (2x s, 6H, CH_3, isoprop), 0.91 (m, 2H, H-6), 0.90 (t, 3H, CH_3, Et), 0.34, 0.33 (2x s, 6H, $SiCH_3$). $^{13}C\{^1H\}$ NMR: δ 139.2 (Cq, arom), 133.2, 128.6, 127.5 (CH, arom), 110.4 (Cq, isoprop), 105.1 (C-1), 81.1, 80.1 (C-2, C-4), 56.9 (C-5), 40.9 (CH_2, Et), 35.0 (C-3), 26.5, 26.0 (CH_3, isoprop), 17.8 (C-6), 15.2 (CH_3, Et), -2.3, -2.4 ($SiCH_3$). *Anal.* calcd for $C_{19}H_{31}NO_3Si$ (*M* 349.21): C, 65.29; H, 8.94; N, 4.01. Found: C, 65.22; H, 8.99; N, 4.00.

5-Amino-6-dimethylphenylsilyl-5-*N*-ethyl-5-*N*-ethyloxycarbonyl-3,5,6-trideoxy-1,2-*O*-isopropylidene-β-L-*lyxo*-hexofuranose (6) - From **5**: Compound **5** (0.95 g, 2.7 mmol) was dissolved in a mixture of 1,4-dioxane (10 mL) and H_2O (5 mL). The solution was cooled (0°C), treated with $NaHCO_3$ (0.49 g, 6.8 mmol) and ethyl chloroformate (0.51 mL, 5.4 mmol). After stirring the resulting mixture for 1 h, the mixture was allowed to warm to rt, concentrated *in vacuo*, and the residue partitioned between Et_2O (50 mL) and H_2O (10 mL). The layers were separated and the organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (Et_2O/light petroleum, 1/5→1/3→1/2, v/v) to give **6** as a colorless oil. Yield 1.00 g (88%). - From **4**: Addition of the cerium reagent **1e** to **4** was performed as described for the preparation of **5**. After the temperature was allowed to warm to rt, ethyl chloroformate (1.59 mL, 16.6 mmol) was added and stirring was continued for 20 min. The mixture was quenched with saturated NaCl-solution (30 mL) and extracted with Et_2O (150 mL). The organic layers were dried ($MgSO_4$) and filtered. After removal of solvents, the residual oil was applied onto a column of silica gel and eluted with Et_2O/light petroleum (1/5 → 1/3 → 1/2, v/v) to give pure **6** as an oil (1.88 g, 81%). R_f 0.7 (Et_2O/light petroleum, 3/1, v/v). ^1H NMR (58°C): δ 7.57-7.51 (m, 2H, H-arom), 7.33-7.21 (m, 3H, H-arom), 5.77 (d, 1H, H-1, $J_{1,2}$ 3.9 Hz), 4.75 (br t, 1H, H-2, $J_{2,3a}$ 4.8 Hz), 4.40 (m, 1H, H-4), 4.19 (br q, 2H, CH_2, OEt, J 6.9 Hz), 3.87 (m, 1H, H-5), 3.46, 3.26 (2x m, 2H, CH_2, NEt), 2.18 (br d, 1H, H-3b, $J_{3a,3b}$ -13.3 Hz), 1.60 (m, 1H, H-3a), 1.47, 1.30 (2x s, 6H, CH_3, isoprop), 1.26, 1.12 (2x t, 6H, CH_3, Et), 0.93 (m, 2H, H-6), 0.36, 0.33 (2x s, 6H, $SiCH_3$). $^{13}C\{^1H\}$ NMR (58°C): δ 158.7 (C=O), 138.3 (Cq, arom), 133.1, 128.6, 127.4 (CH, arom), 110.3 (Cq, isoprop), 104.9 (C-1), 80.3, 80.1 (C-2, C-4), 60.4 (CH_2, OEt), 55.0 (C-5), 38.4 (CH_2, NEt), 36.4 (C-3), 26.4, 25.9 (CH_3, isoprop), 17.2 (C-6), 14.2 (CH_3, Et), -2.9 ($SiCH_3$).

5-Amino-3,5-dideoxy-5-*N*-ethyl-5-*N*-ethyloxycarbonyl-1,2-*O*-isopropylidene-β-L-*lyxo*-hexofuranose (7) - AcOH (25 mL), NaOAc (2.5 g, 30.5 mmol) and KBr (0.51 g, 4.25 mmol) were added to **6** (1.49 g, 3.54 mmol) and the mixture was stirred until the salts were dissolved. The solution was cooled (10°C) and AcO_2H (17.0 mL, 30% in AcOH) was added dropwise under exclusion of light. After the mixture was stirred at 20°C for 2.5 h, the mixture was diluted with Et_2O (100 mL) and poured into a cooled (0°C) solution of $Na_2S_2O_3$ (20 mL, 10%). After separation of the layers, the organic layer was subsequently treated with aqueous $NaHCO_3$ (20 mL) and solid $NaHCO_3$ until no more gas evolved. The layers were separated and the organic layer was washed with H_2O (20 mL). The organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was coevaporated with toluene (2x 10 mL) and applied onto a column of silica gel, which was eluted with EtOAc/light petroleum (3/1→4/1→1/0, v/v). Concentration of the appropriate fractions afforded **7** as an oil. Yield 0.83 g (77%). R_f 0.3 (EtOAc). ^1H NMR (58°C): δ 5.76 (d, 1H, H-1, $J_{1,2}$ 3.9 Hz), 4.73 (br t, 1H, H-2, $J_{2,3a}$ 4.8 Hz), 4.54 (m, 1H, H-4), 4.19 (br q, 2H, CH_2, OEt, J 6.9 Hz), 3.82 (m, 3H, H-5, H-6), 3.48, 3.29 (2x m, 2H, CH_2, NEt), 2.18 (br d, 1H, H-3b, $J_{3a,3b}$ -13.5 Hz), 1.63 (m, 1H, H-3a), 1.48, 1.30 (2x s, 6H, CH_3, isoprop), 1.26, 1.14 (2x t, 6H, CH_3, Et). $^{13}C\{^1H\}$ NMR (58°C): δ 158.2 (C=O), 110.5 (Cq, isoprop), 104.5 (C-1), 79.9, 76.3 (C-2, C-4), 61.2, 60.7 (C-6, CH_2, OEt), 60.9 (C-5), 40.3 (CH_2, NEt), 35.8 (C-3), 26.2, 25.7 (CH_3, isoprop), 14.0 (CH_3, Et).

5-Amino-5-*N*,6-*O*-carbamate-3,5-dideoxy-5-*N*-ethyl-1,2-*O*-isopropylidene-β-L-*lyxo*-hexofuranose (8) - To a cooled (0°C) solution of **7** (0.83 g, 2.74 mmol) in THF (20 mL) was added NaH (0.13 g, 60% in oil). The mixture was stirred at rt for 2 hours, then Et_2O (20 mL) and 15% $NaHCO_3$ (10 mL) were added. The layers were separated, the organic layer was washed with

brine (10 mL) and dried ($MgSO_4$). Concentration under reduced pressure afforded a viscous oil which was crystallized from CH_2Cl_2 to give **8** as white crystals, which were of high enough quality for X-ray analysis. Yield 0.65 g (93%). $[\alpha]_D^{20}$ -19.8 (c 1.0). R_f 0.4 (EtOAc). Mp 115-116°C. MS (m/z): 258 $[M+H]^+$, 280 $[M+Na]^+$, 296 $[M+K]^+$. $^1H\{^1H\}$ NMR (600 MHz): δ 5.84 (d, 1H, H-1, $J_{1,2}$ 3.7 Hz), 4.74 (t, 1H, H-2, $J_{2,3a}$ 4.6 Hz), 4.32 (ddd, 1H, H-4, $J_{3a,4}$ 11.1 Hz, $J_{3b,4}$ 4.3 Hz, $J_{4,5}$ 7.0 Hz), 4.28 (t, 1H, H-6a, $J_{5,6a}$ 8.8 Hz, $J_{6a,6b}$ -8.8 Hz), 3.95 (dd, 1H, H-6b, $J_{5,6b}$ 6.1 Hz), 3.90 (dt, 1H, H-5), 3.55 (dq, 1H, CH_2, Et, *J* 7.2 Hz, -14.4 Hz), 3.35 (dq, 1H, CH_2, NEt, *J* 7.0 Hz, -14.1 Hz), 2.06 (dd, 1H, H-3b, $J_{3a,3b}$ -13.2 Hz, $J_{3b,4}$ 4.3 Hz), 1.54 (ddd, 1H, H-3a), 1.51, 1.32 (2x s, 6H, CH_3, isoprop), 1.19 (t, 3H, CH_3, Et). $^{13}C\{^1H\}$ NMR: δ 158.5 (C=O), 111.1 (Cq, isoprop), 105.6 (C-1), 79.1, 78.8 (C-2, C-4), 62.7 (C-6), 57.0 (C-5), 37.9 (CH_2, Et), 34.3 (C-3), 26.3, 25.7 (CH_3, isoprop), 12.2 (CH_3, Et). *Anal.* calcd for $C_{12}H_{19}NO_5$ (*M* 257.13): C, 56.00; H, 7.45; N, 5.45. Found: C, 55.87; H, 7.54; N, 5.21.

5-Amino-5-*N*,6-*O*-carbamate-3,5-dideoxy-5-*N*-ethyl-L-*lyxo*-hexofuranose (9) - Compound **8** (0.39 g, 1.50 mmol) in 60% aqueous TFA (10 mL) was stirred for 10 min. Concentration under reduced pressure and repeated coevaporation with toluene (5x 2 mL) afforded an oil which was applied onto a column of silica gel. Elution was effected with EtOAc/MeOH (99/1, v/v) to give **9** as amorphous material. Yield 0.30 g (91%). R_f 0.1 (EtOAc). $^{13}C\{^1H\}$ NMR, 9α: δ 158.6 (C=O), 102.5 (C-1), 80.1, 74.7 (C-2, C-4), 63.5 (C-6), 58.8 (C-5), 37.7 (CH_2, Et), 32.7 (C-3), 11.9 (CH_3, Et). 9β: δ 158.5 (C=O), 97.2 (C-1), 77.2, 69.8 (C-2, C-4), 63.4 (C-6), 57.5 (C-5), 37.7 (CH_2, Et), 33.7 (C-3), 11.9 (CH_3, Et).

4-Amino-4-*N*,5-*O*-carbamate-2,4-dideoxy-4-*N*-ethyl-L-*threo*-pentose dimethyl acetal (10) - To a rapidly stirred solution of **9** (0.30 g, 1.38 mmol) in methanol (10 mL) was added a solution of $NaIO_4$ (0.36 g, 1.66 mmol) in H_2O (1.0 mL). Stirring was continued for 2 h, then EtOAc (20 mL) and $MgSO_4$ (5 g) were added, followed by filtration and evaporation of solvents. The residual oil was redissolved in methanol (10 mL), Dowex-H^+ (0.4 g) was added and the mixture was stirred for 20 hours. The mixture was filtered, concentrated under reduced pressure and purified by silica gel column chromatography (EtOAc/light petroleum, 3/1→1/0, v/v) to give, after concentration of the appropriate fractions, pure **10** as an oil. Yield 0.28 g (88%). $[\alpha]_D^{20}$ +5.9 (c 1.0). R_f 0.5 (EtOAc). MS (m/z): 256 $[M+Na]^+$, 202 $[M+H-MeOH]^+$, 234 $[M+H]^+$. ^1H NMR: δ 4.59 (dd, 1H, H-1, $J_{1,2a}$ 5.8 Hz, $J_{1,2b}$ 3.8 Hz), 4.25 (dd, 1H, H-5a, $J_{4,5a}$ 8.8 Hz, $J_{5a,5b}$ 9.2 Hz), 4.19 (dd, 1H, H-5b, $J_{4,5b}$ 5.1 Hz), 4.12 (m, 1H, H-3), 3.92 (dt, 1H, H-4, $J_{3,4}$ 5.1 Hz), 3.54 (dq, 1H, CH_2, Et, *J* 7.3 Hz, -14.1 Hz), 3.42, 3.39 (2x s, 6H, OCH_3), 3.24 (dq, 1H, CH_2, Et, *J* 7.3 Hz, -14.1 Hz), 1.78 (ddd, 1H, H-2a, $J_{2a,2b}$ -14.3 Hz, $J_{2a,3}$ 3.8 Hz), 1.67 (ddd, 1H, H-2b, $J_{2b,3}$ 8.1 Hz), 1.20 (t, 3H, CH_3, Et). $^{13}C\{^1H\}$ NMR: δ 158.1 (C=O), 102.9 (C-1), 67.3 (C-3), 63.4 (C-5), 57.3 (C-4), 53.6, 53.4 (OCH_3), 37.6 (CH_2, Et), 33.2 (C-2), 12.2 (CH_3, Et).

4-Amino-4-*N*,5-*O*-carbamate-2,4-dideoxy-4-*N*-ethyl-3-*O*-methyl-L-*threo*-pentose dimethyl acetal (11) - Alcohol **10** (0.28 g, 1.20 mmol) was rapidly stirred in the dark with Ag_2O (0.42 g, 1.80 mmol), MeI (0.75 mL, 12.0 mmol) and DMF (4 mL) at 40°C for 20 h. Following removal of MeI *in vacuo*, the reaction mixture was diluted with EtOAc (15 mL) and filtered through a pad of Celite. The filtrate was washed with brine (2x 5 mL), dried ($MgSO_4$), filtered and concentrated. The residue was purified by silica gel column chromatography (EtOAc/light petroleum, 1/1→2/1, v/v) to give pure **11**. Yield 0.26 g (88%). $[\alpha]_D^{20}$ -21.9 (c 1.0) (Lit.[7a] -21.2). R_f 0.6 (EtOAc). MS (m/z): 216 $[M+H-MeOH]^+$, 270 $[M+Na]^+$, 286 $[M+K]^+$. ^1H NMR: δ 4.56 (dd, 1H, H-1, $J_{1,2a}$ 6.7 Hz, $J_{1,2b}$ 4.4 Hz), 4.24 (dd, 1H, H-5a, $J_{4,5a}$ 9.2 Hz, $J_{5a,5b}$ -9.2 Hz), 4.13 (dd, 1H, H-5b, $J_{4,5b}$ 5.0 Hz), 4.00

(dt, 1H, H-4, $J_{3,4}$ 5.2 Hz), 3.57 (dq, 1H, CH_2, Et, *J* 7.3 Hz, -14.1 Hz), 3.52 (m, 1H, H-3), 3.40, 3.35, 3.33 (3x s, 9H, OCH_3), 3.15 (dq, 1H, CH_2, Et, *J* 7.3 Hz, -14.1 Hz), 1.78 (ddd, 1H, H-2a, $J_{2a,2b}$ -14.6 Hz, $J_{2a,3}$ 3.6 Hz), 1.69 (ddd, 1H, H-2b, $J_{2b,3}$ 7.9 Hz), 1.19 (t, 3H, CH_3, Et). $^{13}C\{^1H\}$ NMR: δ 158.0 (C=O), 101.5 (C-1), 77.3 (C-3), 63.3 (C-5), 58.0 (OCH_3), 54.6 (C-4), 53.1, 52.9 (OCH_3), 37.6 (CH_2, Et), 31.9 (C-2), 12.4 (CH_3, Et). *Anal.* calcd for $C_{11}H_{21}NO_5$ (*M* 247.14): C, 53.41; H, 8.56; N, 5.67. Found: C, 53.30; H, 8.63; N, 5.60.

References and notes

1. Original manuscript: van Delft, F.L.; van der Marel, G.A.; van Boom, J.H. *Carbohydr. Lett.* **1996**, *in press.*
2. (a) Lee, M.D.; Dunne, T.S.; Siegel, M.M.; Chang, C.C.; Morton, G.O.; Borders, D.B. *J. Am. Chem. Soc.* **1987**, *109*, 3464. (b) Lee, M.D.; Dunne, T.S.; Chang, C.C.; Ellestad, G.A.; Siegel, M.M.; Morton, G.O.; McGahren, W.J.; Borders, D.B. *J. Am. Chem. Soc.* **1987**, *109*, 3466.
3. (a) Nicolaou, K.C.; Smith, A.L.; Yue, E.W. *Proc. Nat. Acad. Sci. USA* **1993**, *90*, 5881. (b) Nicolaou, K.C.; Dai, W.-M. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1387. (c) Lee, M.D.; Ellestad, G.A.; Borders, D.B. *Acc. Chem. Res.* **1991**, *24*, 235. For a review, see: (d) Nicolaou, K.C. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1377. (e) Paloma, L.G.; Smith, J.A.; Chazin, W.J.; Nicolaou, K.C. *J. Am. Chem. Soc.* **1994**, *116*, 3697. (f) Danishefsky, S.J.; Shair, M.D. *J. Org. Chem.* **1996**, *61*, 16.
4. Maier, M.E. *Synlett* **1995**, 13.
5. Zein, N.; Sinha, A.M.; McGahren, W.J.; Ellestad, G.A. *Science* **1988**, *240*, 1198.
6. Walker, S.L.; Andreotti, A.H.; Kahne, D.E. *Tetrahedron* **1995**, *50*, 1351.
7. (a) Groneberg, R.D.; Miyazaki, T.; Stylianides, N.A.; Schulze, T.J.; Stahl, W.; Schreiner, E.P.; Suzuki, T.; Iwabuchi, Y.; Smith, A.L.; Nicolaou, K.C. *J. Am. Chem. Soc.* **1993**, *115*, 7593. (b) Smith, A.L.; Pitsinos, E.N.; Hwang, C.-K.; Mizuno, Y.; Saimoto, H.; Scarlato, G.R.; Suzuki, T.; Nicolaou, K.C. *J. Am. Chem. Soc.* **1993**, *115*, 7612. (c) Nicolaou, K.C.; Hummel, C.W.; Nakada, M.; Shibayama, K.; Pitsinos, E.N.; Saimoto, H.; Mizuno, Y.; Baldenius, K.-U.; Smith, A.L. *J. Am. Chem. Soc.* **1993**, *115*, 7625. (d) Hitchcock, S.A.; Boyer, S.H.; Chu-Moyer, M.Y.; Olson, S.H.; Danishefsky, S.J. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 858.
8. (a) Boons, G.J.P.H.; van der Marel, G.A.; van Boom, J.H. *Tetrahedron Lett.* **1989**, *30*, 229. (b) Boons, G.J.P.H.; Overhand, M.; van der Marel, G.A.; van Boom, J.H. *Carbohydr. Res.* **1989**, *192*, c1-c4. (c) Boons, G.J.P.H.; Overhand, M.; van der Marel, G.A.; van Boom, J.H. *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 1504. (d) Smid, P.; Noort, D.; Broxterman, H.J.G.; van Straten, N.C.R.; van der Marel, G.A.; van Boom, J.H. *Recl. Trav. Chim. Pays-Bas* **1992**, *111*, 524. (e) Smid, P.; Schipper, F.J.M.; Broxterman, H.J.G.; Boons, G.J.P.H.; van der Marel, G.A.; van Boom, J.H. *Recl. Trav. Chim. Pays-Bas* **1993**, *112*, 451.
9. van Delft, F.L.; de Kort, M.; van der Marel, G.A.; van Boom, J.H. *Tetrahedron: Asymmetry* **1994**, *5*, 2261.
10. Nicolaou, K.C.; Groneberg, R.D.; Stylianides, N.A.; Miyazaki, T. *J. Chem. Soc.,*

Chem. Commun. **1990**, 1275.

11. Chatterjee, M.; Smith, P.J.; Townsend, C.A. *J. Org. Chem.* **1996**, *118*, 1938.
12. Barton, D.H.R.; Jang, D.O.; Jaszberenyi, J.C. *Tetrahedron Lett.* **1992**, *33*, 5709.
13. McCarty, C.G. in *The Chemistry of the Carbon-Nitrogen Double Bond*, Patai, S., Ed.; Interscience: London, 1970, pp 363.
14. (a) Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamija, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392. (b) T. Imamoto, in *Comprehensive Organic Synthesis;* Trost, B.M., Fleming, I., Eds.; Pergamon Press, Oxford, 1991, Vol 3, pp 231.
15. Seitz, D.E.; Zapata, A. *Synthesis* **1981**, 557.
16. Addition of methyl chloroformate prior to work-up was also reported for nucleophilic additions to hydrazones: Denmark, S.E.; Weber, T.; Piotrowski, D.W. *J. Am. Chem. Soc.* **1987**, *109*, 2224.
17. Fleming, I.; Sanderson, P.E.J. *Tetrahedron Lett.* **1987**, *28*, 4229.
18. Selected crystallographic data for **8** (colorless crystal from dichloromethane): $C_{12}H_{19}NO_5$, M = 257.28, prismatic (0.2 x 0.2 x 0.5 mm), orthorhombic, space group P $2_12_12_1$; cell parameters: $\underline{a}$ = 9.3174(2), $\underline{b}$ = 11.11750(10), $\underline{c}$ = 12.43490(10) Å, V = 1288.08(3) Å^3, Z = 4, D_c 1.327 g.cm^{-3}, λ (Mo-Kα) = 0.71073 Å, μ = 0.103 mm^{-1}, θ = 2.46 - 28.28°, $-11 \leq h \leq 12$, $-14 \leq k \leq 12$, $-16 \leq l \leq 16$. Data were collected at 198K on a Siemens CCD arla detector mounted on a sealed tube X-ray generator with graphite monochromator using ω-scan mode. Reflections collected = 8079 [R(int) = 0.0476], 2634 reflections with $I>2\sigma(I)$ were classified as independent. Refinement on F_0 by full-matrix least-squares on F^2. Reflections = 3059, restraints = 0, parameters = 240. Goodness-of-fit on F^2 = 1.141, final R = 0.0438, wR = 0.0854, $w = 1/[\sigma^2(F_0^2) + (0.0172P)^2 + 0.4332P]$ where $P = (F_0^2 + 2F_c^2)/3$, $\Delta\rho_{max}$ = 0.172 e.Å^3, $\Delta\rho_{min}$ = -0.177 e.Å^3.
19. Other routes to **12**: (a) Golik, J.; Wong, H.; Vyas, D.M.; Doyle, T.W. *Tetrahedron Lett.* **1989**, *30*, 2497. (b) Kahne, D.; Yang, D.; Lee, M.D. *Tetrahedron Lett.* **1990**, *31*, 21. (c) Mash, E.A.; Nimkar, S.K. *Tetrahedron Lett.* **1993**, *34*, 385. (d) Da Silva, E.; Prandi, J.; Beau, J.-M. *J. Chem. Soc., Chem. Commun.* **1994**, 2127. (e) Roush, W.R.; Hunt, J.A. *J. Org. Chem.* **1995**, *60*, 798.
20. Manna, S.; Viala, J.; Yadagiri, P.; Falck, J.R. *Tetrahedron Lett.* **1986**, *27*, 2679.

VI

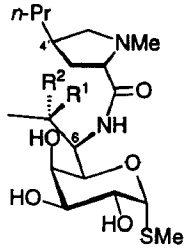
Use of a Novel α-Hydroxyethylating Reagent in the Stereoselective Synthesis of Lincosamine and Clindasamine[1]

Abstract

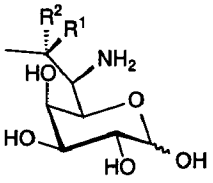
A highly efficient and stereoselective route to the aminoglycoside components of the antibiotics lincomycin (**1a**) and clindamycin (**1b**) is presented. The key step involves simultaneous introduction of two stereogenic centers by a stereospecific copper(I)-mediated condensation of 6-benzylimino-6-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**4**) with 1-(dimethylphenylsilyl)ethylmagnesium chloride (**3d**). The resulting β-amino silane **8** is converted into its 1,2-amino alcohol equivalent *via* oxidative unmasking of the silyl moiety to give protected lincosamine derivative **11** in 61% overall yield based on **4**.

Introduction

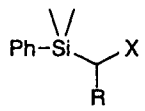
The antibiotic lincomycin (**1a**), isolated[2] from cultures of *Streptomyces lincolnensis* var. *lincolnensis*, inhibits bacterial protein synthesis at ribosomal level by blocking the action of peptidyl transferase[3]. Lincomycin is an effective agent for treatment of Gram-positive bacterial infections[4] although the occurrence of undesired side-effects (*e.g.* pseudomembranoic colitis and nausea) has restricted its application to situations of



1a R^1=OH, R^2=H
b R^1=H, R^2=Cl



2a R^1=OH, R^2=H
b R^1=H, R^2=Cl



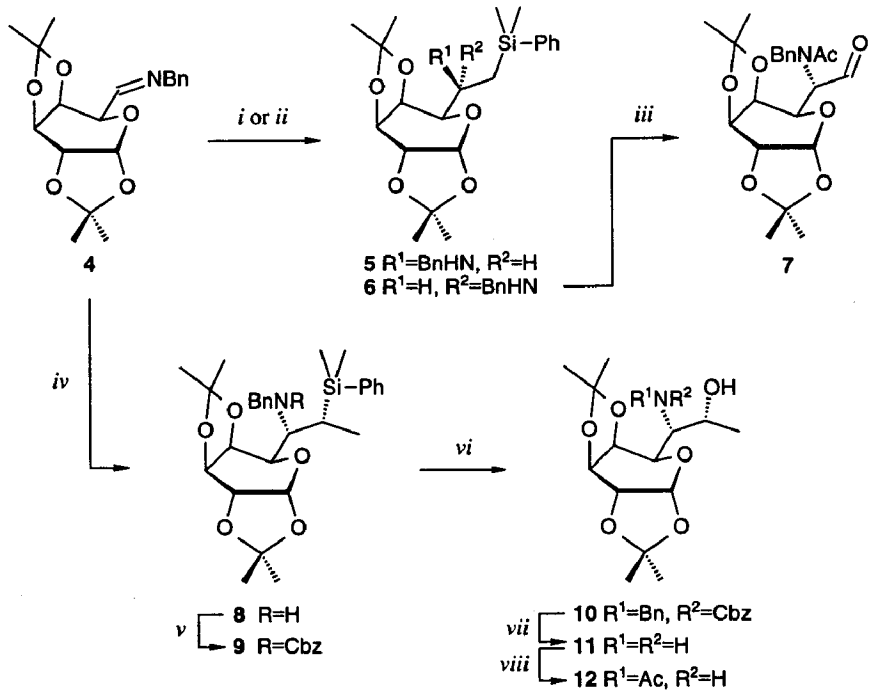
3a R=H, X=Cl
b R=H, X=MgCl
c R=Me, X=Cl
d R=Me, X=MgCl

penicilline resistance or hypersensitivity. Structural studies showed[5] that **1a** consists of a 6-amino-6,8-dideoxyoctose thioglycoside, linked to a C-4' alkylated proline *via* an amide bond. The semi-synthetic 7-chloro analogue clindamycin (**1b**), prepared[6] by chlorination of lincomycin, exhibits similar activity but is much more effective against staphylococci and pneumococci bacteria. Extensive research[7] on the chemical preparation of **1a** has been mainly focussed at lincosamine (**2a**), *i.e.* 6-amino-6,8-dideoxy-D-*erythro*-D-*galacto*-octose, the carbohydrate moiety of lincomycin. Efforts on the total synthesis of **2a** entail the stereocontrolled construction of the pyranose ring using furan-based chemistry[8a,b] or hetero Diels-Alder condensation, as applied[8c] in the first total synthesis of *racemic* lincosamine by Danishefsky *et al.* Syntheses starting from *myo*-inositol[9a] or D-threonine[9b] were also reported recently.

An alternative approach[10] towards the preparation of **2a** comprises C-6 chain-extension of D-galactopyranose. The latter cheap starting material already contains four of the six stereogenic centers present in lincosamine (**2a**). However, a stereoselective preparation of **2a** is rather cumbersome due to the tedious installation of the C-6 amino function with correct configuration. An elegant solution to the problem was independently presented by Knapp[10k] and Stick[10l], entailing intramolecular delivery of a nitrogen nucleophile tethered to the O-4 position. Despite the elegancy of this approach, the efficient assembly of **2a** is hampered by the large number of synthetic steps.

A straightforward procedure to introduce an amino group at C-6 entails nucleophilic addition to galactose imine **4** (Scheme 1). Furthermore, chain-extension of **4** with a two-carbon nucleophile allows for the simultaneous introduction of C-7 and C-8. Atsumi[10f] and Bose[10m], however, reported that the nucleophilic addition proceeds with *syn*-stereoselectivity, resulting in the predominant or exclusive formation of the undesired C-7 epimer. On the other hand, earlier work from our laboratory revealed[12] that (dimethylphenylsilyl)methylmagnesium chloride (**3b**), derived from commercially available silane **3a**, is an effective reagent for the stereoselective hydroxymethylation of 6-benzylimino-6-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**4**, Scheme 1). For example, addition of **3b**, precomplexed with cerium(III) chloride, to imine **4** led to the exclusive formation of the *syn*-adduct **5**. On the other hand, complete reversal of stereochemistry was attained by executing the same reaction with the corresponding organocopper reagent, prepared *in situ* by precomplexation of **3b** with CuI and $BF_3{\cdot}Et_2O$. The resulting *anti*-adduct **6** could then be transformed into α-amino aldehyde **7**, which is a known precursor of lincosamine (**2a**). Although installation of the C-6 amino function proceeds with the desired stereoselectivity for the synthesis of lincosamine, it is evident that conversion of aldehyde **7** into **2a** demands the creation of an additional stereogenic center at C-7 by stereoselective methylation[10f]. The stereochemical outcome of the copper(I)-mediated condensation of **3b** with **4** stimulated us to find out whether the required stereogenic centers could be introduced in one step by α-hydroxyethylation of **4** with the secondary Grignard reagent 1-(dimethylphenylsilyl)ethylmagnesium chloride (**3d**).

Scheme 1



Reagents and conditions

(*i*) **3b**, $CeCl_3$, Et_2O, THF, -78°C → 0°C, 8 h (68%); (*ii*) **3b**, CuI, $BF_3{\cdot}Et_2O$, -70°C → -20°C, 6 h (70%); (*iii*) (a) Ac_2O, $NaHCO_3$, 1,4-dioxane, H_2O, 0.5 h (b) KBr, AcO_2H, NaOAc, AcOH, 2 h. (3) DMSO, $(COCl)_2$, CH_2Cl_2, -60°C, 1 h then Et_3N, -60°C → 0°C (65%); (*iv*) **3d**, CuI, $BF_3{\cdot}Et_2O$, -70°C → -20°C, 6 h (84%); (*v*) CbzCl, $NaHCO_3$, 1,4-dioxane, H_2O, 0.5 h (88%); (*vi*) KBr, AcO_2H, NaOAc, AcOH, 3h (82%); (*vii*) H_2, $Pd(OH)_2$, MeOH (100%); (*viii*) Ac_2O, $NaHCO_3$, 1,4-dioxane, H_2O, 0.5 h (84%).

Results and Discussion

The Grignard reagent **3d** was readily accessible in two steps from commercially available (chloromethyl)dimethylphenylsilane (**3a**). α-Deprotonation[13] and methylation of the thus obtained anion of **3a** afforded crude (1-chloroethyl)dimethylphenylsilane (**3c**). Work-up of the reaction mixture, followed by purification on silica gel and distillation, gave racemic **3c** in more than 95% purity, as gauged by proton NMR spectroscopy. Metallation of **3c** with magnesium gave the secondary Grignard reagent **3d**. At this stage, a solution of the benzylimine derivative **4** (Scheme 1) in THF was added dropwise to a cooled (-70°C) suspension of the organocopper derivative of **3d** (2.5 equiv.), prepared[14] by sequential complexation of **3d** with stoichiometric amounts of copper(I) iodide and $BF_3{\cdot}Et_2O$. The reaction mixture was kept at -70°C for 1 hour, slowly warmed to -20°C and quenched with excess triethylamine. Extractive work-up and purification by silica gel column chromatography gave, as evidenced by high resolution NMR spectroscopy, a

homogeneous and diastereomerically pure product in 84% yield. The newly introduced C-6 and C-7 stereocenters in the β-amino silane adduct were established to have the respective S and R configuration as in **8** (Scheme 1) by its transformation into the known[10f] protected lincosamine derivative **12**. In order to avoid N-oxidation during unmasking of the silyl moiety in the next step, the amino group was further protected with a benzyloxycarbonyl group (**8**→**9**). Unmasking of fully protected **9** with potassium bromide in peracetic acid[15] afforded amino alcohol **10** in 82% yield. Conversion of **10** into **12** was accomplished by the following two-step procedure. Hydrogenolysis of benzyl and benzyloxycarbonyl protecting groups and subsequent selective N-acetylation of **11** under Schotten-Bauman conditions gave **12** in an overall yield of 84% after purification. The thus obtained product was in all aspects identical (melting point, optical rotation, NMR data) to the same compound prepared previously[10g].

The excellent stereoselectivity observed in the condensation of **3d** and **4** can be rationalized as follows. It may be assumed that the condensation of imine **4** with the organocopper reagent derived from **3d**, as in the copper(I)-mediated *anti*-addition of **3b** to **4**, proceeds according to the Felkin-Anh model[16] (Figure 1). In line with this model, aldimine **4** adopts a conformation[17] having a torsion angle of -90° between the C-N double bond and the ring oxygen (O-5). Attack of the nucleophile occurs from the sterically least hindered side, *i.e.* the *re*-face of the imine. However, the orientation of **3d** in the sterically most favorable transition state geometry is strongly influenced by the bulkiness of its substituents[18,19]. It is most likely that in a matched pair transition state the least hindered position will be occupied by the sterically most congested silyl moiety (Figure 1). In addition, an *exo*-like orientation of the methyl group in the nucleophile will minimize steric interactions with the sugar[20].

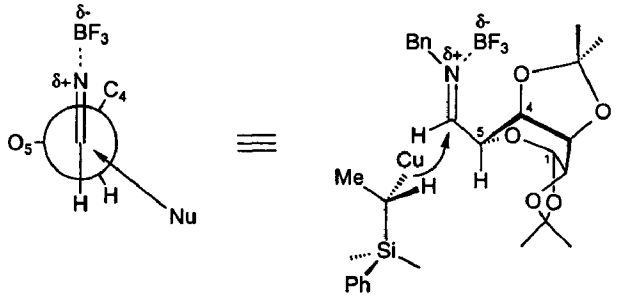
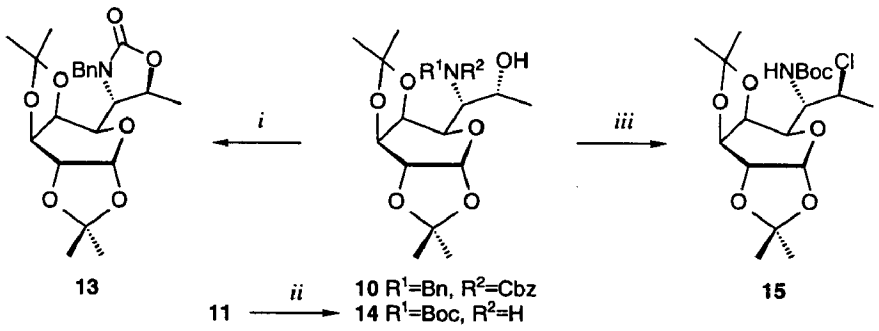


Figure 1. Schematic presentation of the Felkin-Anh model for nucleophilic addition of **3d** to imine **4** (left) and the presumed in space orientation of reactants (right).

At this stage, attention was focussed on the synthesis of clindasamine (**2b**). Due to the free alcohol function at C-7 in derivative **10**, conversion of **10** to **2b** may be achieved *via* chlorination with inversion of configuration. However, subjection of **10** to several chlorinating procedures (CCl_4/PPh_3[21], $SOCl_2$/2,6-lutidine[22], $ZnCl_2$/DEAD/PPh_3[23]) was

abortive. On the other hand, treatment of **10** with the highly reactive combination[24] of triphenylphosphine and hexachloroethane resulted in the rapid (8 min) disappearance of starting material and formation of a more lipophilic product. NMR analysis of the homogeneous compound, obtained after work-up and purification (95% yield), indicated the sole formation, with inversion of configuration at C-7 (Scheme 2), of 2-oxazolidinone **13**[25]. The latter result may be rationalized by a concerted mechanism entailing intramolecular nucleophilic attack of the carbonyl oxygen at the developing cationic center at C-7 with concomitant liberation of benzyl chloride. In order to prevent the cyclization to the 2-oxazolidinone **13**, the *tert*-butoxycarbonyl group was applied to protect the amine at C-6. Thus, the aminofunction of **11**, obtained earlier by hydrogenolysis of **10**, was

Scheme 2



Reagents and conditions

(*i*) PPh_3, C_2Cl_6, $C_2H_4Cl_2$, 10 min (95%); (*ii*) Boc_2O, $NaHCO_3$, 1,4-dioxane, H_2O, 15 h (77%); (*iii*) PPh_3, C_2Cl_6, $C_2H_4Cl_2$, 1 h (80%).

was selectively protected with Boc_2O under Schotten-Bauman conditions, to give **14** in good yield. Treatment of **14** with triphenylphosphine/hexachloroethane afforded a single product, unambiguously identified as chloride **15** by spectroscopic techniques (NMR, MS). No traces of a 2-oxazolidinone were detected, indicating that cyclization was effectively prevented by introduction of the Boc-protective group.

Conclusion

A valuable intermediate (**11**) in the synthesis of lincomycin has been prepared in an efficient and concise route using the readily accessible α-hydroxyethylating reagent **3d**[26]. The latter result presents, to the best of our knowledge, the first example of the successful application of a secondary organocopper reagent in the diastereoselective addition to an imine. Furthermore, the unexpected formation of compound **13** from amino alcohol **10** may be of value for the future preparation of 2-oxazolidinones with inversion of configuration.

Experimental

General methods and materials - Toluene was distilled from P_2O_5 and stored over 4Å MS, THF and Et_2O were freshly distilled from $LiAlH_4$. MeOH (HPLC-grade, Rathburn), 1,4-dioxane and AcOH were used as received. Triethylamine was distilled from CaH_2. All reactions were performed under strictly anhydrous conditions unless noted otherwise. Reactions were followed by TLC analysis on Schleicher and Schüll DC Fertigfolien F 1500 LS 254. Compounds were visualized by UV light (254 nm) and by spraying with 20% H_2SO_4 in MeOH followed by charring at 140°C, amines were charred with ninhydrin. Column chromatography was performed on silica gel 60, 230-400 mesh (Merck). Optical rotations were measured in $CHCl_3$ on a Propol automatic polarimeter. Mass spectra (FAB) were recorded on a Finnigan MAT TSQ70 triple quadrupole mass spectrometer. ^1H NMR spectra and ^{13}C NMR spectra (50.1 MHz) were recorded using a Jeol JNM-FX 200 spectrometer, unless noted otherwise. ^1H NMR spectra (300 MHz) were recorded using a Bruker WM-300 spectrometer and ^1H NMR spectra (600 MHz) were recorded using a Bruker 600-DMX spectrometer. Chemical shifts (δ) are given in ppm relative to tetramethylsilane. (Chloromethyl)dimethylphenylsilane was purchased from Aldrich Chemical Co. and used as received.

(1-Chloroethyl)dimethylphenylsilane (3c) - (Chloromethyl)dimethylphenylsilane (9.02 mL, 50 mmol) in THF (80 mL) at -78°C under nitrogen was treated with *s*-BuLi (42.3 mL, 1.3 M), followed by *N,N,N',N'*-tetramethylethylenediamine (8.3 mL, 55 mmol). After the mixture was kept at -78°C for 40 min, the solution was warmed (-40°C) and MeI (3.42 mL, 55 mmol) added. After 30 min, the reaction mixture was allowed to warm to rt, quenched with a 15% NH_4Cl solution (50 mL) and extracted with light petroleum (200 mL). The organic layer was washed with H_2O (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography (light petroleum) and vacuum distillation to afford **3c** as a colorless liquid. Yield 8.05 g (81%). Bp 52-54°C (15 mmHg). ^1H NMR: δ 7.58-7.33 (m, 5H, H-arom), 3.53 (q, 1H, H-1, $J_{1,2}$ 7.5 Hz), 0.71 (d, 3H, H-2), 0.27, 0.25 (2x s, 6H, $SiCH_3$). $^{13}C\{^1H\}$ NMR: δ 141.0 (Cq, arom), 134.1, 129.6, 127.8 (CH, arom), 44.9 (C-1), 20.0 (C-2), -5.0, -6.2 ($SiCH_3$).

6-Benzylimino-6-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (4) - To a cooled (-60°C) solution of oxalyl chloride (1.05 ml, 12.0 mmol) in CH_2Cl_2 (60 ml) was added dropwise a mixture of DMSO (1.42 ml, 20 mmol) in CH_2Cl_2 (20 ml). Subsequently, a solution of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranoside (2.08 g, 8.0 mmol) in CH_2Cl_2 (15 ml) was added dropwise and the reaction mixture was stirred at -60°C for 30 min. Et_3N (4.15 ml, 30 mmol) was added to the reaction mixture which was kept at -60°C for another 30 min before it was allowed to warm to rt. After 30 min, the mixture was diluted with CH_2Cl_2 (50 ml) and washed with H_2O (2x 20 ml). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The crude aldehyde thus obtained was dissolved in toluene (50 ml) and cooled (0°C) before $MgSO_4$ (2.41 g) and $BnNH_2$ (1.31 ml, 12 mmol) were added. After 16 h, the reaction mixture was filtered, concentrated under reduced pressure and purified by flash chromatography (elution: Et_2O/light petroleum/Et_3N, 40/60/1→50/50/1→60/40/1, v/v/v) to give **4** as a slightly yellow oil. Yield 2.72 g (98%). R_f 0.5 (CH_2Cl_2/aceton/Et_3N, 95/5/1, v/v/v). ^1H NMR: δ 7.75 (d, 1H, H-6, $J_{5,6}$ 3.9 Hz), 7.37-7.24 (m, 5H, H-arom), 5.61 (d, 1H, H-1, $J_{1,2}$ 4.9 Hz), 4.67-4.43 (m, 5H, H-3, H-4, H-5, CH_2, Bn), 4.34 (dd, 1H, H-2, $J_{2,3}$ 2.3 Hz), 1.53, 1.48, 1.34, 1.33 (4x s, 12H, CH_3, isoprop). $^{13}C\{^1H\}$ NMR: δ 163.4 (C-6), 138.2 (Cq, arom), 127.9, 127.5, 126.5 (CH, arom), 108.9, 108.2 (Cq, isoprop), 95.7 (C-1), 72.9, 70.2, 70.0, 69.5 (C-2, C-3, C-4, C-5), 64.2 (CH_2, Bn), 25.6, 25.5, 24.5, 23.9 (CH_3, isoprop).

6-Benzylamino-6,7,8-trideoxy-7-dimethylphenylsilyl-1,2:3,4-di-*O*-isopropylidene-D-*erythro*-α-

D-*galacto*-octopyranose (8) - Under an argon atmosphere, a suspension of magnesium powder (0.34 g, 13.8 mmol) in refluxing THF (2 mL) was activated by addition of a few drops of 1,2-dibromoethane. Next, a solution of **3c** (2.38 g, 12.5 mmol) in THF (10 mL) was added at such a rate as to maintain a gentle reflux. The mixture was kept at 40°C for 1 h before the addition of THF (10 mL) and cooling to -40°C. Under a stream of argon, solid CuI (2.38 g, 12.5 mmol) was added with vigorous stirring. After 30 min, the heterogeneous mixture was cooled to -70°C and $BF_3{\cdot}Et_2O$ (1.53 mL, 12.5 mmol) was added. After 5 min, a solution of **4** (1.74 g, 5.0 mmol) in THF (5 mL) was added slowly to the mixture which was kept at -70°C for 1 h before slow warming to -20°C. The reaction was quenched with excess Et_3N and poured into a vigorously stirred solution of aqueous NH_4Cl (30 mL, 15%). Et_2O (100 mL) was added and the organic layer was washed with H_2O (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The oily product was applied onto a column of silica gel and eluted with light petroleum followed by Et_2O/light petroleum/Et_3N (20/80/1→40/60/1→60/40/1, v/v/v) to give **8** as an oil. Yield 2.15 g (84%). R_f 0.4 (Et_2O/light petroleum/Et_3N, 70/30/1, v/v/v). $[\alpha]_D^{20}$ -38.8 (c 1). MS (m/z): 512 $[M+H]^+$. ^1H NMR (600 MHz): δ 7.56-7.12 (m, 10H, H-arom), 5.55 (d, 1H, H-1, $J_{1,2}$ 5.2 Hz), 4.58 (d, 1H, H-3, $J_{3,4}$ 8.1 Hz), 4.49 (d, 1H, H-4), 4.26 (dd, 1H, H-2, $J_{2,3}$ 1.5 Hz), 3.89, 3.67 (AB, 2H, CH_2, Bn, J -12.7 Hz), 3.61 (d, 1H, H-5, $J_{5,6}$ 9.4 Hz), 3.13 (dd, 1H, H-6, $J_{6,7}$ 2.1 Hz), 1.73 (dq, 1H, H-7, $J_{7,8}$ 7.6 Hz), 1.50, 1.45, 1.33, 1.31 (4x s, 12H, CH_3, isoprop), 1.00 (d, 3H, H-8), 0.37, 0.35 (2x s, 6H, $SiCH_3$). $^{13}C\{^1H\}$ NMR: δ 141.1, 138.7 (Cq, arom), 133.8, 128.7-126.6 (CH, arom), 108.4, 107.8 (Cq, isoprop), 96.7 (C-1), 71.2, 71.1, 70.7, 67.8 (C-2, C-3, C-4, C-5), 53.3 (CH_2, Bn), 25.9, 25.8, 24.7, 24.2 (CH_3, isoprop), 20.6 (C-8), 7.4 (C-7), -3.4, -3.9 ($SiCH_3$). *Anal.* calcd for $C_{29}H_{41}NO_5Si$ (*M* 511.74): C, 68.07; H, 8.08; N, 2.74. Found: C, 67.31; H, 8.04; N, 2.68.

6-(*N*-Benzyloxycarbonyl)benzylamino-6,7,8-trideoxy-7-dimethylphenylsilyl-1,2:3,4-di-*O*-isopropylidene-D-*erythro*-α-D-*galacto*-octopyranose (9) - Compound **8** (2.0 g, 3.91 mmol) was dissolved in a mixture of 1,4-dioxane (20 mL) and H_2O (10 mL). The solution was cooled (0°C), treated with $NaHCO_3$ (0.71 g, 9.8 mmol) and benzyl chloroformate (0.73 mL, 4.3 mmol). The mixture was allowed to reach rt and stirred for 1 h. The mixture was concentrated and the residue was partitioned between Et_2O (50 mL) and H_2O (10 mL). The layers were separated, the organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography (elution: toluene/EtOAc, 10/1→5/1→3/1→1/1, v/v) to give **9** as a colorless oil. Yield 2.22 g (88%). R_f 0.7 (toluene/EtOAc, 5/1, v/v). $[\alpha]_D^{20}$ -37.6 (c 2). MS (m/z): 646 $[M+H]^+$, 668 $[M+Na]^+$. $^{13}C\{^1H\}$ NMR (58°C): δ 139.0, 136.3 (Cq, arom), 133.0-126.9 (CH, arom), 108.4, 108.3 (Cq, isoprop), 96.4 (C-1), 71.2, 70.4 (C-2, C-3, C-4, C-5), 67.0 (CH_2, Cbz), 64.8 (CH_2, Bn), 59.4 (C-6), 25.8, 24.8, 23.9 (CH_3, isoprop), 20.8 (C-8), -2.4 ($SiCH_3$). *Anal.* calcd for $C_{37}H_{47}NO_7Si$ (*M* 645.87): C, 68.81; H, 7.34; N, 2.17. Found: C, 68.51; H, 7.38; N, 2.10.

6-(*N*-Benzyloxycarbonyl)benzylamino-6,8-dideoxy-1,2:3,4-di-*O*-isopropylidene-D-*erythro*-α-D-*galacto*-octopyranose (10) - NaOAc (3.2 g, 3.9 mmol) was dissolved in AcOH (30 mL) and added to **9** (2.05 g, 3.17 mmol). KBr (0.45 g, 3.8 mmol) was added, the solution was cooled (10°C) and AcOOH (15.9 mL, 30% in AcOH) was added dropwise under exclusion of light. After stirring for 3 h at 20°C, the mixture was diluted with Et_2O (100 mL) and poured into a cooled (0°C) solution of $Na_2S_2O_3$ (30 mL, 10%). The organic layer was washed with aqueous $NaHCO_3$ (10 mL, 15%) and treated with solid $NaHCO_3$ until no more gas evolved. The layers were separated and the organic layer was extracted with H_2O (20 mL), dried ($MgSO_4$) and concentrated. The residue was coevaporated with toluene (2x 10 mL) before silica gel column chromatography (elution: toluene/EtOAc, 95/5→85/15, v/v). Concentration of the appropriate fractions gave **10** as an oil. Yield 1.37 g (82%). R_f 0.3 (toluene/EtOAc, 5/1, v/v). $[\alpha]_D^{20}$ -63.4 (c 1). MS (m/z): 528 $[M+H]^+$.

$^{13}C\{^1H\}$ NMR (58°C): δ 156.1 (C=O), 137.6, 136.2 (Cq, arom), 128.7-127.3 (CH, arom), 108.8 (Cq, isoprop), 96.2 (C-1), 70.7-69.9 (C-2, C-3, C-4, C-5, C-7), 67.2 (CH_2, Cbz), 54.1 (CH_2, Bn), 25.8, 25.7, 24.8, 24.1 (CH_3, isoprop), 20.0 (C-8). *Anal.* calcd for $C_{29}H_{37}NO_8$ (*M* 527.62): C, 66.02; H, 7.07; N, 2.66. Found: C, 66.02; H, 7.11; N, 2.74.

6-Amino-6,8-dideoxy-1,2:3,4-di-*O*-isopropylidene-D-*erythro*-α-D-*galacto*-octopyranose (11) - Compound **10** (0.57 g, 1.08 mmol) was dissolved in MeOH (6 mL), $Pd(OH)_2$ (0.1 g, 20%) was added and the suspension was kept under a H_2-atmosphere (1 atm) for 1 h. The catalyst was removed by filtration over Celite and washed with MeOH. The combined filtrates were concentrated *in vacuo* to give **11** as a white solid. Yield 0.33 g (100%). R_f 0.2 (EtOAc/MeOH, 19/1, v/v). Mp 74-76°C. $[\alpha]_D^{20}$ -51.9 (c 2). MS (m/z): 304 $[M+H]^+$, 326 $[M+Na]^+$. ^1H NMR (300 MHz): δ 5.51 (d, 1H, H-1, $J_{1,2}$ 5.1 Hz), 4.62 (dd, 1H, H-3, $J_{2,3}$ 2.5 Hz, $J_{3,4}$ 8.0 Hz), 4.44 (dd, 1H, H-4, $J_{4,5}$ 1.8 Hz), 4.32 (dd, 1H, H-2), 4.03 (dq, 1H, H-7, $J_{6,7}$ 4.8 Hz, $J_{7,8}$ 6.4 Hz), 3.59 (dd, 1H, H-5, $J_{5,6}$ 9.1 Hz), 3.13 (dd, 1H, H-6), 1.53, 1.46, 1.36, 1.33 (4x s, 12H, CH_3, isoprop), 1.18 (d, 3H, H-8). $^{13}C\{^1H\}$ NMR: δ 108.8, 108.2 (Cq, isoprop), 96.1 (C-1), 70.8, 70.3, 70.0, 68.4, 66.8 (C-2, C-3, C-4, C-5, C-7), 54.4 (C-6), 25.6, 25.5, 24.5, 24.2 (CH_3, isoprop), 16.2 (C-8). *Anal.* calcd for $C_{14}H_{25}NO_6$ (*M* 303.36): C, 55.43; H, 8.31; N, 4.62. Found: C, 55.23; H, 8.39; N, 4.51.

6-Acetamido-6,8-dideoxy-1,2:3,4-di-*O*-isopropylidene-D-*erythro*-α-D-*galacto*-octopyranose (12) - To a stirred solution of **11** (0.10 g, 0.34 mmol) in a mixture of 1,4-dioxane (2 mL) and H_2O (2.5 mL) was added $NaHCO_3$ (67 mg, 0.85 mmol) and Ac_2O (0.032 mL, 0.68 mmol). After 1 h, the mixture was concentrated and coevaporated with toluene (3x 2 mL). The residue was purified by flash chromatography (elution: EtOAc) to give **12** as a colorless oil, which was crystallized from Et_2O. Yield 98 mg (84%). Mp 166-167°C (Lit.[10g] 166-167°C). R_f 0.4 (EtOAc/MeOH, 19/1, v/v). $[\alpha]_D^{20}$ -51.4 (c 2) (Lit.[10g] -53). ^1H NMR (300 MHz): δ 5.53 (d, 1H, H-1, $J_{1,2}$ 5.0 Hz), 4.61 (dd, H-3, $J_{2,3}$ 2.3 Hz, $J_{3,4}$ 8.0 Hz), 4.45 (dd, 1H, H-4, $J_{4,5}$ 1.1 Hz), 4.30 (dd, 1H, H-2), 4.17-4.10 (m, 1H, H-5), 4.03 (m, 1H, H-7), 3.91 (d, 1H, H-6, $J_{6,7}$ 4.5 Hz), 1.99 (s, 3H, CH_3, Ac), 1.73 (br s, 1H, OH), 1.52, 1.50, 1.35, 1.32 (4x s, 12H, CH_3, isoprop), 1.24 (d, 3H, H-8, $J_{7,8}$ 6.4 Hz). $^{13}C\{^1H\}$ NMR: δ 170.6 (C=O), 109.1, 108.7 (Cq, isoprop), 96.5 (C-1), 71.8, 70.8, 70.4, 68.2, 65.2 (C-2, C-3, C-4, C-5, C-7), 56.4 (C-6), 25.8, 24.8, 24.1 (CH_3, isoprop), 23.3 (CH_3, Ac), 19.8 (C-8). *Anal.* calcd for $C_{16}H_{27}NO_7$ (*M* 345.39): C, 55.64; H, 7.88; N, 4.06. Found: C, 55.60; H, 7.91; N, 4.01.

6-Amino-6-*N*-benzyl-6-*N*,7-*O*-carbamate-6,8-dideoxy-1,2:3,4-di-*O*-isopropylidene-L-*threo*-α-D-*galacto*-octopyranose (13) - To a solution of **10** (0.16 g, 0.30 mmol) in 1,2-dichloroethane (3 ml) at rt was added PPh_3 (0.16 g, 0.60 mmol), followed by a solution of C_2Cl_6 (0.14 g, 0.60 mmol) in 1,2-dichloroethane (2 ml). After 8 min, Et_3N (0.12 ml, 1.20 mmol) was added, solvents were evaporated and the residue, in CH_2Cl_2 (1 mL) was applied onto a column of silica gel, which was eluted with Et_2O/light petroleum (1/1→2/1, v/v) to give **13** as a colorless oil. Yield 0.12 g (95%). R_f 0.4 (Et_2O/light petroleum, 3/1, v/v). $[\alpha]_D^{20}$ -62.1 (c 1). MS (m/z): 420 $[M+H]^+$, 442 $[M+Na]^+$. ^1H NMR (300 MHz): δ 7.34-7.24 (m, 5H, H-arom), 5.49 (d, 1H, H-1, $J_{1,2}$ 5.1 Hz), 4.93, 4.10 (AB, 2H, CH_2, Bn, *J* -14.8 Hz), 4.62 (dd, 1H, H-3, $J_{2,3}$ 2.4 Hz, $J_{3,4}$ 7.9 Hz), 4.61 (dq, 1H, H-7, $J_{6,7}$ 3.0 Hz, $J_{7,8}$ 6.7 Hz), 4.30 (dd, 1H, H-2), 4.17 (dd, 1H, H-4, $J_{4,5}$ 1.8 Hz), 3.77 (dd, 1H, H-5, $J_{5,6}$ 6.4 Hz), 3.25 (dd, 1H, H-6), 1.53, 1.44, 1.36, 1.33 (s, CH_3, isoprop), 1.14 (d, 3H, H-8). $^{13}C\{^1H\}$ NMR: δ 158.2 (C=O), 136.5 (Cq, arom), 128.5, 128.1, 127.7 (CH, arom), 109.4, 108.9 (Cq, isoprop), 96.3 (C-1), 73.2, 70.9, 70.8, 70.4 (C-2, C-3, C-4, C-5), 66.6 (C-7), 60.2 (C-6), 46.5 (CH_2, Bn), 26.0, 25.6, 24.7, 24.2 (CH_3, isoprop), 20.6 (C-8).

6-Amino-6-*N*-*tert*-butoxycarbonyl-6,8-dideoxy-1,2:3,4-di-*O*-isopropylidene-D-*erythro*-α-D-

***galacto*-octopyranose (14)** - Compound **11** (0.20 g, 0.66 mmol) was dissolved in a mixture of 1,4-dioxane (3 mL) and H_2O (4 mL), then $NaHCO_3$ (0.11 g, 1.32 mmol) and a solution of Boc_2O (0.17 g, 0.79 mmol) were added successively. After 20 h, Et_2O (15 mL) was added, the layers were separated and the organic layer washed with H_2O (3 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (Et_2O/light petroleum, 1/2→1/1, v/v) to give **14**. Yield 0.21 g (77%). R_f 0.6 (Et_2O). $[\alpha]_D^{20}$ -42.2 (c 2). ^1H NMR: δ 5.54 (d, 1H, H-1, $J_{1,2}$ 4.9 Hz), 4.59 (dd, 1H, H-3, $J_{2,3}$ 2.4 Hz, $J_{3,4}$ 7.9 Hz), 4.42 (d, 1H, H-4), 4.29 (dd, 1H, H-2), 4.05 (m, 2H, H-5, H-7), 3.82 (m, 1H, H-6), 1.52, 1.48, 1.34, 1.33 (4x s, 12H, CH_3, isoprop) 1.43 (s, 9H, CH_3, Boc), 1.24 (d, 3H, H-8, $J_{7,8}$ 6.5 Hz). $^{13}C\{^1H\}$ NMR: δ 156.1 (C=O), 109.1, 108.5 (Cq, isoprop), 96.4 (C-1), 71.5, 70.7, 70.4, 68.4 (C-2, C-3, C-4, C-5, C-7), 56.6 (C-6), 28.2 (CH_3, Boc), 25.8, 25.7, 24.8, 24.2 (CH_3, isoprop), 22.0 (H-8).

6-Amino-6-*N*-*tert*-butoxycarbonyl-7-chloro-6,7,8-trideoxy-1,2:3,4-di-*O*-isopropylidene-L-*threo*-α-D-*galacto*-octopyranose (15) - Compound **14** (0.21 g, 0.47 mmol) was treated with PPh_3 and C_2Cl_6 as described for the preparation of **13**. Yield 0.18 g (80%). R_f 0.5 (Et_2O/light petroleum, 3/1, v/v). MS (m/z): 422 $[M+H]^+$. ^1H NMR: δ 5.50 (d, 1H, H-1, $J_{1,2}$ 4.7 Hz), 4.70 (m, 3H, H-2, H-3, H-4), 4.29 (m, 2H, H-2, H-5), 4.05 (m, 1H, H-7), 3.82 (dd, 1H, H-6, $J_{5,6}$ 1.5 Hz, $J_{6,7}$ 9.7 Hz), 1.54, 1.52, 1.32 (3x s, 12H, CH_3, isoprop), 1.45 (s, 9H, CH_3, Boc), 1.30 (s, 3H, H-8). $^{13}C\{^1H\}$ NMR: δ 157.2 (C=O), 109.3, 108.7 (Cq, isoprop), 96.2 (C-1), 71.0, 70.6, 70.2, 67.5 (C-2, C-3, C-4, C-5), 59.2 (C-7), 53.9 (C-6), 28.2 (CH_3, Boc), 25.9, 24.9, 24.0 (CH_3, isoprop), 21.8 (H-8).

References and notes

1. Published in part: van Delft, F.L.; de Kort, M.; van der Marel, G.A.; van Boom, J.H. *J. Org. Chem.* **1996**, *61*, 1883.
2. Hoeksema, H.; Bannister, B.; Birkenmeyer, R.D.; Magerlein, B.J.; MacKellar, F.A.; Schroeder, W.; Slomp, G.; Herr, R.R. *J. Am. Chem. Soc.* **1964**, *86*, 4223.
3. Douthwaite, S. *Nucl. Acids Res.* **1992**, *20*, 4717.
4. Wright, J.L.C. *The lincomycin-celesticetin-anthramycin group* in *Biochemistry and Genetic Regulation of Commercially Important Antibiotics*, Vining, L.C. (ed.), London: Addison-Wesley, 1983, pp. 311.
5. Slomp, G.; MacKellar, F.A. *J. Am. Chem. Soc.* **1967**, *89*, 2454.
6. Magerlein, B.J.; Birkenmeyer, R.D.; Kagan, F. *Antibacterial Agents Chemotherapy* **1966**, 727.
7. For a recent review: Gołebiowski, A.; Jurczak, J. *Total Synthesis of Lincomycin and Related Chemistry* in *Recent Progress in the Chemical Synthesis of Antibiotics*, Springer Verlag, Berlin-Heidelberg, 1990.
8. (a) Gołebiowski, A.; Jurczak, J. *Tetrahedron* **1991**, *47*, 1045. (b) Szechner, B.; Achmatowicz, O. *Pol. J. Chem.* **1994**, *68*, 1149. (c) Danishefsky, S.J.; Larson, E.; Springer, J.P. *J. Am. Chem. Soc.* **1985**, *107*, 1274.
9. (a) Chida, N.; Nakazawa, K.; Ninomiya, S.; Amano, S.; Koizumi, K.; Inaba, J.; Ogawa, S. *Carbohydrate Lett.* **1995**, *1*, 335. (b) Marshall, J.A.; Beaudoin, S. *J. Org. Chem.* **1996**, *61*, 581.
10. (a) Magerlein, B.J. *Tetrahedron Lett.* **1970**, 33. (b) Howarth, G.B.; Lance, D.G.; Szarek, W.A.; Jones, J.K.N. *Can. J. Chem.* **1969**, *47*, 75. (c) Howarth, G.B.; Szarek,

W.A.; Jones, J.K.N. *J. Chem. Soc. C* **1970**, 2218. (d) Saeki, H.; Ohki, E. *Chem. Pharm. Bull.* **1970**, *18*, 789. (e) Hems, R.; Horton, D.; Nakadate, M. *Carbohydr. Res.* **1972**, *25*, 205. (f) Atsumi, T.; Fukumaru, T.; Matsui, M. *Agr. Biol. Chem.* **1973**, *37*, 2627. (g) Woolard, G.R.; Rathbone, E.B.; Szarek, W.A.; Jones, J.K.N. *J. Chem. Soc., Perkin Trans 1* **1976**, 950. (h) Gateau-Olesker, A.; Sepulchre, A.M.; Vass, G.; Géro, S.D. *Tetrahedron* **1977**, *33*, 393. (i) Hoppe, I.; Schöllkopf, U. *Liebigs Ann. Chem.* **1980**, 1474. (j) Czernecki, S.; Valéry, J.-M. *J. Carbohydr. Chem.* **1990**, *9*, 767. (k) Knapp, S.; Kukkola, P.J. *J. Org. Chem.* **1990**, *55*, 1632. (l) Engelhardt, L.M.; Skelton, B.W.; Stick, R.V.; Tilbrook, D.M.G.; White, A.H. *Aust. J. Chem.* **1990**, *43*, 1657. (m) Bose, A.K.; Mathur, C.; Wagle, D.R.; Naqvi, R.; Manhas, M.S. *Heterocycles* **1994**, *39*, 491.

11. High stereocontrol in addition of organometallics to galactose nitrone was reported. Dondoni, A.; Franco, S.; Merchan, F.; Merino, P.; Tejero, T. *Synlett* **1993**, 78.
12. van Delft, F.L.; de Kort, M.; van der Marel, G.A.; van Boom, J.H. *Tetrahedron: Asymmetry* **1994**, *5*, 2261.
13. Burford, C.; Cooke, F.; Ehlinger, E.; Magnus, P. *J. Am. Chem. Soc.* **1977**, *99*, 4536.
14. Wada, M.; Sakurai, Y.; Akiba, K. *Tetrahedron Lett.* **1984**, *25*, 1079.
15. Fleming, I.; Sanderson, P.E.J. *Tetrahedron Lett.* **1987**, *28*, 4229.
16. (a) Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199. (b) Anh, N.T. *Top. Curr. Chem.* **1980**, *88*, 145.
17. The pyranose ring of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose adopts a skew-boat conformation. Midland, M.M.; Asirwatham, G.; Cheng, J.C.; Miller, J.A.; Morell, L.A. *J. Org. Chem.* **1994**, *59*, 4438.
18. A similar reasoning was followed to explain the stereochemistry of nucleophilic addition of the anion of benzyltriphenylsilane to a chiral epoxide. Corey, E.J.; Chen, Z. *Tetrahedron Lett.* **1994**, *35*, 8731.
19. Acyclic copper(I) reagents exist in dynamic equilibrium. Linderman, R.J.; Griedel, B.D. *J. Org. Chem.* **1991**, *56*, 5491.
20. $BF_3{\cdot}Et_2O$-mediated nucleophilic addition of a secondary anion to an α-alkoxy imine was reported to give an 1,2-amino alcohol with *syn*-stereoselectivity. Based on ^{13}C NMR data, however, the assigned configuration is most likely incorrect. (a) Green, D.L.C.; Kiddle, J.J.; Thompson, C.M. *Tetrahedron* **1995**, *51*, 2865. It was also shown that the α-boryl ethyl carbanion adds to benzaldehyde predominantly with *anti*-selectivity (ratio 6:1). The diastereoselectivity was explained by a transition state geometry highly similar to the one depicted in Figure 1. (b) Sakai, M.; Saito, S.; Kanai, G.; Suzuki, A.; Miyaura, N. *Tetrahedron* **1996**, *52*, 915.
21. Appel, R. *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 801.
22. Tabushi, I.; Tamary, Y.; Yoshida, Z. *Tetrahedron Lett.* **1970**, 2931.
23. Rollin, P. *Synth. Commun.* **1986**, *16*, 611.
24. Appel, R.; Willms, L. *Chem. Ber.* **1977**, *110*, 3209.
25. ^{13}C NMR analysis of trans-oxazolidinone **13** showed a lower chemical shift for C-7 than for the cis-analogue, obtained by treatment of **10** with NaH in THF.
26. α-Hydroxyallylation of aldehydes using metallated allylaminosilane has also been reported. Tamao, K.; Nakajo, E.; Ito, Y. *J. Org. Chem.* **1987**, *52*, 957.

VII

Preparation of 2-Oxazolidinones by Intramolecular Nucleophilic Substitution[1]

Abstract

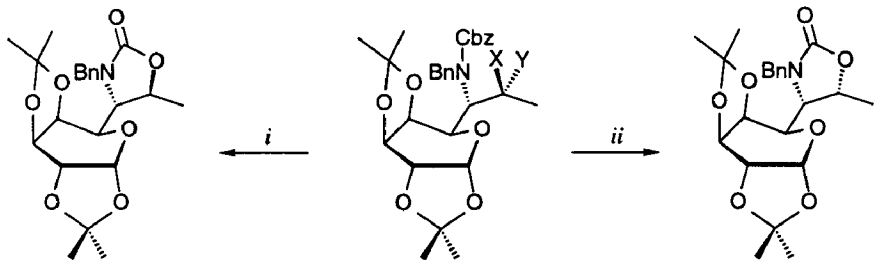
Treatment of *N*-benzyl,*N*-alkyloxycarbonyl protected β-amino alcohols with triphenylphosphine and hexachloroethane in 1,2-dichloroethane induces cyclization. The 2-oxazolidinones are formed by intramolecular nucleophilic attack with inversion of configuration at the secondary alcohol. In contrast, subjection of monoprotected urethanes to the same conditions leads to chlorination.

Introduction

As part of a program to prepare rare sugar components of biologically active compounds we recently showed[2] that hydroxymethylation of α-alkoxy imines is a useful procedure for the diastereoselective preparation of destomic acid and lincosamine. Further extension of this methodology led to the finding that amino alcohol **1**, a precursor of the antibiotic lincomycin[3a], can be prepared in excellent diastereoselective fashion *via* α-hydroxyethylation of suitably protected 6-benzylimino galactose[4].

It was anticipated that the C-7 chlorinated derivative of lincomycin, *i.e.* clindamycin[3b], could be obtained by conversion of **1** into **2** (Scheme 1). Initial attempts aimed at the transformation of **1** into **2** embraced treatment of **1** with PPh_3 in CCl_4 or with $SOCl_2$. However, these chlorinating conditions led to complete recovery of starting material. The same disappointing result was obtained using PPh_3 and $ZnCl_2$, *i.e.* Mitsunobu conditions[5] for alcohol displacement. On the other hand, subjection of **1** to a mixture of PPh_3 and

Scheme 1



3a | **1** X=H, Y=OH; **2** X=Cl, Y=H | **3b**

Reagents and conditions

(*i*) PPh_3, C_2Cl_6, $C_2H_4Cl_2$ (95%); (*ii*) NaH, THF (94%).

C_2Cl_6 in 1,2-dichloroethane[6] resulted in rapid (9 min) conversion of starting material into a more lipophilic product, as indicated by TLC analysis. Structure analysis of the product (NMR, MS) showed, however, the exclusive formation of 2-oxazolidinone **3a** (95% yield). During cyclization, inversion of configuration at C-7 had occurred, as ascertained[7] by comparison of ^{1}H NMR data of **3a** with those of epimeric compound **3b**, obtained by treatment of **1** with NaH in THF.

With the objective to investigate the potential usefulness of this new transformation, the structurally related substrates **4a-d** were subjected to the PPh_3/C_2Cl_6 mixture. Treatment of **4a** with triphenylphosphine and hexachloroethane afforded a single product, identified as 2-oxazolidinone **5a** by NMR and MS analysis. Also in this case, the cyclocarbamation to **5a** had occurred with inversion of configuration, as indicated by the opposite optical rotation of **5a** as compared to that of ent-**5a**, prepared from **4a** by base treatment. Similarly, cyclization of substrates **4b-d** to the corresponding 2-oxazolidinones **5b-d** proceeded cleanly (Table 1). It is of interest to note that the cyclization was not affected by the nature of the urethane alkyl group (R) in terms of yield and reaction rate, *i.e.* no difference was observed in reaction of **4b** and **4d** (R=Bn) as compared to **4b'** and **4d'** (R=Et). On the other hand, it was found that transformation of **4d** into known[8] bicyclic **5d** only took place at elevated temperature and after prolonged reaction time. The scope of the method is further illustrated in the synthesis of the strained sugar 2-oxazolidinones **7** and **9** (Scheme 2), obtained in excellent yield by cyclocarbamation of easily accessible urethanes **6** and **8**, respectively. The stereochemical identity of **7** and **9** was established by comparison of NMR data with those of authentic **7** and **9**, prepared *via* an alternative route.

Similar transformation of β-amino alcohol derivatives to 2-oxazolidinones with inversion of configuration was described by Kano *et al.*[9a] in the cyclization of *N*-benzyloxycarbonyl protected vicinal hydroxyl amines of type **10** (Table 2) upon

Table 1. Preparation of 2-oxazolidinones **5a-d**.

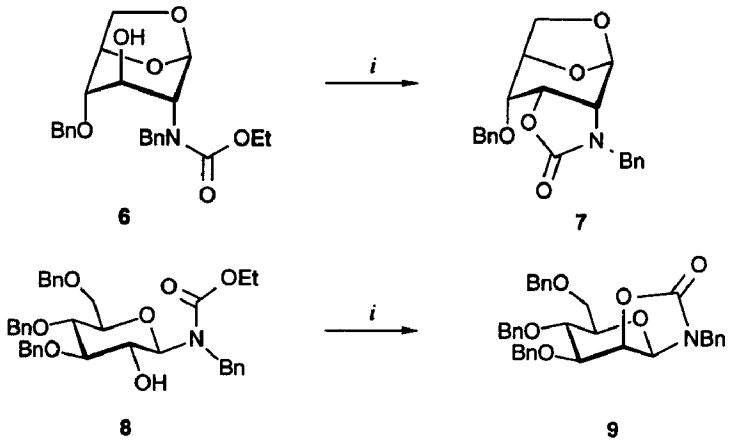
4 **5**

Entry	Starting Compound	R	R^1	R^2	R^3	Product	Yield (%)	Time
1	**4a**	Bn	Me	H	H	**5a**	98	1 h
2	**4b**	Bn	Ph	H	Me	**5b**	99	8 min
3	**4b'**	Et	Ph	H	Me	**5b**	99	7 min
4	**4c**	Bn	H	Ph	Me	**5c**	86	10 min
5	**4d**	Bn	H	$-(CH_2)_4-$		**5d**	88	16 h[a]
6	**4d'**	Et	H	$-(CH_2)_4-$		**5d**	89	16 h[a]

[a]Reaction performed at 50°C.

treatment with Tf_2O or with thionyl chloride at elevated temperature. A fluoride-induced assembly of 2-oxazolidinones from similar Cbz-protected β-amino alcohols was reported by Ohfune *et al.*[9b] following a three-step approach comprising *O*-sulfonylation, *N*-protective group interconversion ($CO_2Bn \rightarrow CO_2TBS$) and treatment with TBAF. More recently, rearrangement of *N*-Boc protected β-amino alcohols was observed upon

Scheme 2



Reagents and conditions

(*i*) PPh_3, C_2Cl_6, $C_2H_4Cl_2$ (**7**: 86%, **9**: 86%).

tosylation[9a] or triflation[9b] of the hydroxyl function. In order to investigate the scope of the PPh_3/C_2Cl_6-mediated cyclization of monoprotected urethanes to 2-oxazolidinones, compounds **10a-d** (Table 2) were subjected to the above described reaction conditions. In contrast with earlier observations, NMR and mass spectroscopic data of the reaction products indicated the formation of chlorides **11a-d**. In this respect it has to be noted that formation of compound **11d** proceeded sluggishly (16 h) and treatment of **10b** resulted in a mixture of diastereomeric chlorides **11b** and **11c** (ratio ≈ 1:1). The latter observation can be ascribed to facile racemization of the initially formed benzylic chloride (**11b**→**11c**).

Table 2. Preparation of chlorides **11a-d**.

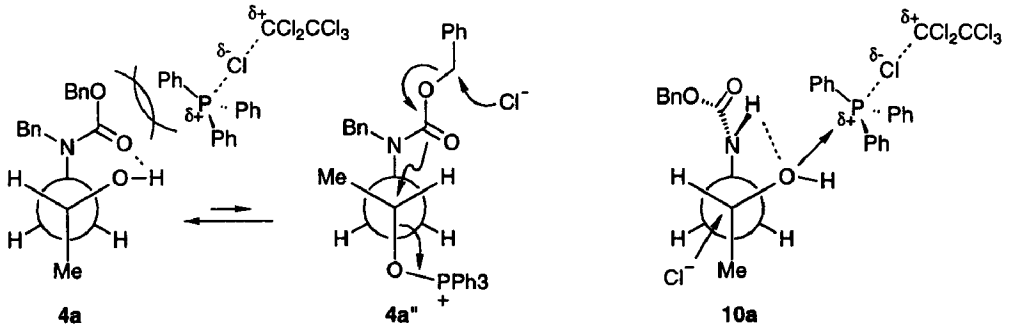
10 **11**

Entry	Starting Compound[a]	R^1	R^2	R^3	Product(s)	Yield (%)	Time
1	**10a**	Me	H	H	**11a**	91	4 min
2	**10b**	Ph	H	Me	**11b+11c**	46[a]	8 min
3	**10d**	H	$-(CH_2)_4-$		**11d**	82	16 h

[a]Combined yield of **11b** and **11c** (R^1=H, R^2=Ph, R^3=Me).

The striking difference between the PPh_3/C_2Cl_6 mediated conversion of bis- and monoprotected urethanes, leading to 2-oxazolidinones or chlorides, may be rationalized as follows. As illustrated for (*R*)-1-amino-2-propanol (Figure 1), the C-O and C-N bonds of secondary and primary urethane **4a** and **10a**, respectively, may adopt a hydrogen bonded gauche orientation in the ground state. In the first step of the reaction, the alcoholic function in **4a** or **10a** attacks the positively charged phosphorous[10] in the complex of PPh_3 and C_2Cl_6. Subsequent rearside attack of Cl^-, liberated from C_2Cl_6, leads to the formation of chloride **11a** from **10a**. On the other hand, destabilization of the phenylphosphonium intermediate of **4a** by increased steric interactions of PPh_3 with the urethane moiety may induce 120° rotation around the bond between C-1 and C-2, leading to the energetically favoured rotamer **4a''** (Figure 1). Subsequent intramolecular attack of the urethane carbonyl oxygen at the developing cationic centre at C-2 with concomitant formation of benzyl chloride *via* S_N2 substitution at the benzyl position leads to the formation of **5a**. Moreover, the electron donating character of the additional alkyl *N*-substituent in **4a** may enhance the nucleophilicity of the carbonyl oxygen[11].

Figure 1. Newman presentation of the transition states for the conversion of **4a** and **10a** into 2-oxazolidinone **5a** and chloride **11a**, respectively.



Conclusion

A highly efficient procedure is described for the cyclization of *N*-alkylated urethanes to 2-oxazolidinones, which in turn may give access to valuable chiral amino alcohols.

Experimental

General methods and materials - Toluene was distilled from P_2O_5 and stored over 4Å molecular sieves, THF and Et_2O were freshly distilled from $LiAlH_4$. Reactions were performed under anhydrous conditions unless noted otherwise. Reactions were followed by TLC analysis on Schleicher and Schüll DC Fertigfolien F 1500 LS 254. Compounds were visualized by UV light (254 nm) followed by spraying with 20% sulfuric acid in methanol and charring at 140°C, amines were charred with ninhydrin. Column chromatography was performed on silica gel 60, 230-400 mesh (Merck). Optical rotations were measured in $CHCl_3$ on a Propol automatic polarimeter. Mass spectra were recorded on a Finnigan MAT TSQ70 triple quadrupole mass spectrometer (EI or FAB). ^1H NMR spectra and ^{13}C NMR spectra (50.1 MHz) were recorded using a Jeol JNM-FX 200 spectrometer, unless stated otherwise. ^1H NMR Spectra (300 MHz) were recorded using a Bruker WM-300 spectrometer. Chemical shifts (δ) are given in ppm relative to tetramethylsilane as internal standard. (*R*)-(-)-1-Amino-2-propanol, (1*R*,2*S*)-(+)-norephedrine and *trans*-2-aminocyclohexanol hydrochloride were obtained from Aldrich and used as received.

Typical procedure for treatment with PPh_3 and C_2Cl_6 - To a solution of a protected 1,2-amino alcohol (1 mmol) in 1,2-dichloroethane (5 mL) at rt was added PPh_3 (2 mmol), followed by a solution of C_2Cl_6 in 1,2-dichloroethane (2 mL). When the reaction was complete, the solution was concentrated *in vacuo*, dissolved in a minimal amount of CH_2Cl_2 and immediately applied onto a column of silica gel. Elution was effected with Et_2O/light petroleum.

6-Benzylamino-6-*N*,7-*O*-carbamate-6,8-dideoxy-1,2:3,4-di-*O*-isopropylidene-L-*threo*-α-D-*galacto*-octopyranose (3a) - Yield 95%. R_f 0.4 (Et_2O/light petroleum, 3/1, v/v). $[\alpha]_D^{20}$ -62.1 (c 1). MS (EI, m/z): 422, 279, 424. ^1H NMR: δ 7.34-7.24 (m, 5H, H-arom), 5.49 (d, 1H, H-1, $J_{1,2}$ 5.1 Hz), 4.93, 4.10 (AB, 2H, CH_2, Bn, J -14.8 Hz), 4.62 (dd, 1H, H-3, $J_{2,3}$ 2.4 Hz, $J_{3,4}$ 7.9 Hz), 4.61

(dq, 1H, H-7, $J_{6,7}$ 3.0 Hz, $J_{7,8}$ 6.7 Hz), 4.30 (dd, 1H, H-2), 4.17 (dd, 1H, H-4, $J_{4,5}$ 1.8 Hz), 3.77 (dd, 1H, H-5, $J_{5,6}$ 6.4 Hz), 3.25 (dd, 1H, H-6), 1.53, 1.44, 1.36, 1.33 (4x s, 12H, CH_3, isoprop), 1.14 (d, 3H, H-8). $^{13}C\{^1H\}$ NMR: δ 158.2 (C=O), 136.5 (Cq, arom), 128.5, 128.1, 127.7 (CH, arom), 109.4, 108.9 (Cq, isoprop), 96.3 (C-1), 73.2, 70.9, 70.8, 70.4 (C-2, C-3, C-4, C-5), 66.6 (C-7), 60.2 (C-6), 46.5 (CH_2, Bn), 26.0, 25.6, 24.7, 24.2 (CH_3, isoprop), 20.6 (C-8).

6-Benzylamino-6-*N*,7-*O*-carbamate-6,8-dideoxy-1,2:3,4-di-*O*-isopropylidene-D-*erythro*-α-D-*galacto*-octopyranose (3b) - Compound **1**[4] (88 mg, 0.17 mmol) in THF (2 mL) was treated with NaH (8 mg, 60% in oil) and stirred for 1 h. There was added Et_2O (10 mL) and a saturated solution of NH_4Cl (2 mL, 15%). The layers were separated and the organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was applied onto a column of silica gel and elution effected with Et_2O/light petroleum (2/1, v/v) to give **3b** as an oil. Yield 66 mg (94%). R_f 0.6 (toluene/EtOAc, 3/2, v/v). $[\alpha]_D^{20}$ -48.3 (c 1). ^1H NMR: δ 7.38-7.26 (m, 5H, H-arom), 5.49 (d, 1H, H-1, $J_{1,2}$ 5.1 Hz), 4.89, 4.32 (AB, 2H, CH_2, Bn, J -14.9 Hz), 4.64 (dd, 1H, H-3, $J_{2,3}$ 2.3 Hz, $J_{3,4}$ 7.9 Hz), 4.50 (sept, 1H, H-7, $J_{6,7}$ $J_{7,8}$ 6.8 Hz), 4.30 (dd, 1H, H-2), 4.26 (dd, 1H, H-4, $J_{4,5}$ 1.5 Hz), 3.91 (dd, 1H, H-5, $J_{5,6}$ 9.0 Hz), 3.60 (dd, 1H, H-6), 1.53, 1.46, 1.42, 1.32 (4x s, 12H, CH_3, isoprop), 1.47 (d, 3H, H-8). $^{13}C\{^1H\}$ NMR: δ 159.2 (C=O), 137.4 (Cq, arom), 128.5, 127.8, 127.6 (CH, arom), 109.1, 108.7 (Cq, isoprop), 96.4 (C-1), 76.2, 70.7, 70.4, 70.0 (C-2, C-3, C-4, C-5), 64.6 (C-7), 56.1 (C-6), 47.3 (CH_2, Bn), 25.8, 25.6, 24.6, 24.2 (CH_3, isoprop), 15.2 (C-8).

*Typical procedure for the synthesis of compounds **4a-d*** - To a cooled (0°C) solution (suspension) of the amine (hydrochloride) (1 mmol) in toluene (5 mL) was added $MgSO_4$ (0.12 g), Et_3N (1.5 or 2.5 mmol) and benzaldehyde (0.12 mL, 1.2 mmol) and the mixture was stirred overnight. Solids were filtered off and the solvent evaporated *in vacuo*. The residue was redissolved in MeOH (5 mmol), cooled (0°C) and treated with $NaBH_4$ (42 mg, 1.1 mmol). After 2 h at rt, acetone (1 mL) was added, and solids were filtered off over Celite. The residue was concentrated under reduced pressure and redissolved in a mixture of 1,4-dioxane (3 mL) and H_2O (2 mL) before the addition of $NaHCO_3$ (0.17 g, 2 mmol) and an alkyl chloroformate (1.3 mmol). When the reaction was complete, the mixture was diluted with Et_2O (20 mL) and the layers separated. The organic phase was washed with brine (3 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The oil thus obtained was purified by silica gel column chromatography to give compounds **4a-d**.

(*R*)-1-(*N*-Benzyloxycarbonyl)benzylamino-2-propanol (4a) - R_f 0.4 (Et_2O). $[\alpha]_D^{20}$ -10.9 (c 1.0). ^1H NMR (58°C): δ 7.31-7.21 (m, 10H, H-arom), 5.18 (s, 2H, CH_2, Cbz), 4.58 (s, 2H, CH_2, Bn), 4.02 (m, 1H, H-2), 3.4-3.1 (m, 3H, H-1, OH), 1.12 (d, 3H, H-3, $J_{2,3}$ 6.2 Hz). $^{13}C\{^1H\}$ NMR (58°C): δ 156.8 (C=O), 137.2, 136.2 (Cq, arom), 128.2-126.8 (CH, arom), 66.9 (CH_2, Cbz), 66.1 (C-2), 54.3 (C-1), 51.2 (CH_2, Bn), 20.5 (C-3).

(1*R*,2*S*)-*N*-Benzyl-*N*-benzyloxycarbonyl-norephedrine (4b) - R_f 0.8 (Et_2O/light petroleum, 3/1, v/v). $[\alpha]_D^{20}$ +11.7 (c 2). ^1H NMR (58°C): δ 7.30-7.22 (m, 15H, H-arom), 5.05 (s, 2H, CH_2, Cbz), 4.94 (br s, 1H, H-1), 4.20 (AB, CH_2, Bn, J -14.1 Hz), 3.51 (m, 1H, H-2), 1.15 (d, 3H, H-3, $J_{2,3}$ 7.3 Hz). $^{13}C\{^1H\}$ NMR (58°C): δ 156.3 (C=O), 142.3, 137.9, 136.0 (Cq, arom), 128.0-125.6 (CH, arom), 75.7 (C-1), 66.8 (CH_2, Cbz), 60.7 (C-2), 50.6 (CH_2, Bn), 11.2 (C-3).

(1*R*,2*S*)-*N*-Benzyl-*N*-ethyloxycarbonyl-norephedrine (4b') - R_f 0.8 (Et_2O/light petroleum, 3/1, v/v). $[\alpha]_D^{20}$ +11.7 (c 2). ^1H NMR (58°C): δ 7.34-7.21 (m, 10H, H-arom), 4.92 (br s, 1H, H-1), 4.22 (q, 2H, CH_2, Et), 3.51 (m, 1H, H-2), 1.29 (t, 3H, CH_3, Et), 1.16 (d, 3H, H-3, $J_{2,3}$ 7.1 Hz). $^{13}C\{^1H\}$ NMR (58°C): δ 156.6 (C=O), 142.4, 137.8 (Cq, arom), 128.1-125.6 (CH, arom), 76.1 (C-1), 61.2

(CH_2, Et), 61.0 (C-2), 51.0 (CH_2, Bn), 14.3 (C-3), 11.7 (CH_3, Et).

(±)-*trans*-2-(*N*-Benzyloxycarbonyl)benzylaminocyclohexanol (4d) - R_f 0.7 (Et_2O). ^1H NMR (58°C): δ 7.33-7.20 (m, 10H, H-arom), 5.18 (s, 2H, CH_2, Cbz), 4.50 (AB, CH_2, Bn, J -13.8 Hz), 3.83-3.58 (m, 2H, H-1, H-2), 2.10-1.18 (m, 8H, H-3, H-4, H-5, H-6). $^{13}C\{^1H\}$ NMR: δ 157.0 (C=O), 139.0, 136.6 (Cq, arom), 128.0-126.6 (CH, arom), 70.2 (C-1), 66.9 (CH_2, Cbz), 63.3 (C-2), 48.0 (CH_2, Bn), 34.8, 29.6 (C-3, C-6), 25.1, 24.1 (C-4, C-5).

(±)-*trans*-2-(*N*-Ethyloxycarbonyl)benzylaminocyclohexanol (4d') - R_f 0.7 (Et_2O). ^1H NMR (58°C): δ 7.31-7.23 (m, 5H, H-arom), 4.48 (AB, CH_2, Bn, J -13.7 Hz), 4.18 (q, 2H, CH_2, Et), 3.81-3.60 (m, 2H, H-1, H-2), 2.12-1.13 (m, 8H, H-3, H-4, H-5, H-6). $^{13}C\{^1H\}$ NMR (58°C): δ 157.1 (C=O), 139.4 (Cq, arom), 128.0, 127.0, 126.6 (CH, arom), 70.1 (C-1), 63.3 (C-2), 61.0 (CH_2, Et), 48.2 (CH_2, Bn), 34.9, 29.7 (C-3, C-6), 25.2, 24.2 (C-4, C-5), 14.3 (CH_3, Et).

(1*S*,2*S*)-*N*-Benzyl-*N*-ethyloxycarbonyl-norephedrine (4c) - Compound **5b** (0.44 g, 1.65 mmol) was dissolved in 1,4-dioxane (10 mL) and aqueous LiOH (10 mL, 1M) was added. The mixture was refluxed for 48 h, cooled to rt, diluted with Et_2O (30 mL) and the layers were separated. The organic phase was washed with brine (5 mL), dried ($MgSO_4$), filtered and concentrated. The oily residue was purified by column chromatography (elution: Et_2O/light petroleum, 1/1→2/1, v/v) to give (1*S*,2*S*)-*N*-benzyl-norephedrine. Yield 0.37 g (94%). R_f 0.3-0.5 (Et_2O/light petroleum, 3/1, v/v). $^{13}C\{^1H\}$ NMR: δ 142.5, 140.0 (Cq, arom), 128.7-126.0 (CH, arom), 77.4 (C-1), 59.0 (C-2), 50.9 (CH_2, Bn), 16.1 (C-3). Treatment of the benzylamine with ethyl chloroformate and work-up was executed as described in the general procedure for the synthesis of **4a-d**, to give **4c** as a colorless oil. Yield 0.44 g (91%). R_f 0.8 (Et_2O/light petroleum, 3/1, v/v). $[\alpha]_D^{20}$ +74.6 (c 2). ^1H NMR (58°C): δ 7.32-7.22 (m, 10H, H-arom), 4.70 (dd, 1H, H-1, $J_{1,2}$ 5.8 Hz), 4.51, 4.20 (AB, 2H, CH_2, Bn, J -15.8 Hz), 4.19 (q, 2H, CH_2, Et), 3.90 (m, 1H, H-2), 1.25 (t, 3H, CH_3, Et), 1.07 (d, 3H, H-3, $J_{2,3}$ 7.0 Hz). $^{13}C\{^1H\}$ NMR (58°C): δ 157.2 (C=O), 142.3, 138.5 (Cq, arom), 128.0-126.3 (CH, arom), 76.2 (C-1), 61.1 (CH_2, Et), 59.7 (C-2), 50.2 (CH_2, Bn), 15.2 (C-3), 14.2 (CH_3, Et).

(*R*)-3-Benzyl-5-methyl-2-oxazolidinone (ent-5a) - Treatment of **4a** (0.14 g, 0.45 mmol) with NaH was executed as described in the preparation of **3b** to give the title compound as an oil. Yield 83 mg (95%). $[\alpha]_D^{20}$ +22.1 (c 1.0).

Cyclization of compounds 4a-d - Treatment of compounds **4a-c** with PPh_3 and C_2Cl_6 was executed as described in the general procedure to give 2-oxazoldinones **5a-d**. Conversion of **4d** and **4d'** was executed at 50°C.

(*S*)-3-Benzyl-5-methyl-2-oxazolidinone (5a) - R_f 0.3 (Et_2O). $[\alpha]_D^{20}$ -22.3 (c 1.0). MS (EI, m/z): 91, 104, 191. ^1H NMR: δ 7.36-7.24 (m, 5H, H-arom), 4.61 (m, 1H, H-2), 4.42 (AB, 2H, CH_2, Bn, J -18.2 Hz), 3.49 (dd, 1H, H-1a, $J_{1a,1b}$ -8.4 Hz, $J_{1a,2}$ 8.4 Hz), 2.97 (dd, 1H, H-1b, $J_{1b,2}$ 7.0 Hz), 1.39 (d, 3H, H-3, $J_{2,3}$ 5.3 Hz). $^{13}C\{^1H\}$ NMR: δ 157.6 (C=O), 135.6 (Cq, arom), 128.6, 127.8, 127.7 (CH, arom), 69.9 (C-2), 50.5 (C-1), 48.0 (CH_2, Bn), 20.4 (C-3).

(4*S*,5*S*)-3-Benzyl-4-methyl-5-phenyl-2-oxazolidinone (5b) - R_f 0.4 (Et_2O/light petroleum, 3/1, v/v). $[\alpha]_D^{20}$ -61.7 (c 1). MS (EI, m/z): 118, 91, 267. ^1H NMR: δ 7.39-7.24 (m, 10H, H-arom), 4.93 (d, 1H, H-1, $J_{1,2}$ 7.9 Hz), 4.82, 4.17 (AB, 2H, CH_2, Bn, J -15.4 Hz), 3.47 (dq, 1H, H-2, $J_{2,3}$ 6.2 Hz), 1.28 (d, 3H, H-3). $^{13}C\{^1H\}$ NMR: δ 157.6 (C=O), 135.5, 134.5 (Cq, arom), 128.7-125.8 (CH, arom), 82.3 (C-1), 58.3 (C-2), 45.8 (CH_2, Bn), 17.1 (C-3).

(4*S*,5*R*)-3-Benzyl-4-methyl-5-phenyl-2-oxazolidinone (5c) - R_f 0.4 (toluene/EtOAc, 19/1, 1/1). $[\alpha]_D^{20}$ -14.6 (c 2). MS (EI, m/z): 91, 118, 267. ^{1}H NMR: δ 7.41-7.21 (m, 10H, H-arom), 5.51 (d, 1H, H-1, $J_{1,2}$ 8.1 Hz), 4.89, 4.01 (AB, 2H, CH_2, Bn, J -15.2 Hz), 3.90 (dq, 1H, H-2, $J_{2,3}$ 6.6 Hz), 0.72 (d, 3H, H-3). ^{13}C{^{1}H} NMR: δ 157.6 (C=O), 135.5, 134.5 (Cq, arom), 128.2-125.6 (CH, arom), 78.0 (C-1), 53.6 (C-2), 45.2 (CH_2, Bn), 13.6 (C-3).

(±)-*cis*-1-Benzyl-3-oxaperhydro-2-indolinone (5d) - R_f 0.9 (Et_2O). MS (EI, m/z): 91, 150, 231. ^{1}H NMR: δ 7.38-7.26 (m, 5H, H-arom), 4.78, 4.04 (AB, 2H, CH_2, Bn, J -15.1 Hz), 4.46 (dt, 1H, H-1, $J_{1,2}$ 6.7 Hz, $J_{1,6}$ 5.1 Hz), 3.49 (dt, 1H, H-2, $J_{2,3a}$ 5.3 Hz, $J_{2,3b}$ 6.7 Hz), 2.03-1.17 (m, 8H, H-3, H-4, H-5, H-6). ^{13}C{^{1}H} NMR: δ 158.6 (C=O), 136.0 (Cq, arom), 128.4, 127.8, 127.5 (CH, arom), 73.1 (C-1), 53.2 (C-2), 45.4 (CH_2, Bn), 26.6, 25.0, 19.3, 19.2 (C-3, C-4, C-5, C-6).

1,6-Anhydro-4-*O*-benzyl-2-(*N*-ethyloxycarbonyl)benzylamino-2-deoxy-β-D-glucopyranose (6) - A mixture of 1,6:2,3-dianhydro-4-*O*-benzyl-β-D-mannopyranose[12] (0.53 g, 2.28 mmol), benzylamine (0.37 mL, 3.42 mmol) and *i*-PrOH (6 mL) was heated in a sealed tube for 4 d at 120°C. Upon cooling the solution, a white solid precipitated which was filtered off, rinsed with *i*-PrOH and dried *in vacuo* to give 1,6-anhydro-4-*O*-benzyl-2-benzylamino-2-deoxy-β-D-glucopyranose. Yield 0.75 g (97%). $[\alpha]_D^{20}$ -34.8 (c 0.5). Mp 176-178°C. ^{1}H NMR ($CDCl_3$, MeOD): δ 7.32-7.26 (m, 10H, H-arom), 5.54 (br s, 1H, H-1), 4.65 (s, 2H, CH_2, OBn), 4.54 (br d, 1H, H-5), 4.12-3.70 (m, 6H, H-3, H-4, H-6, CH_2, NBn), 3.30 (s, 1H, H-2). ^{13}C{^{1}H} NMR ($CDCl_3$, MeOD): δ 137.5 (Cq, arom), 128.2-126.8 (CH, arom), 101.7 (C-1), 78.1, 73.7, 67.2 (C-3, C-4, C-5), 71.2 (CH_2, OBn), 65.0 (C-6), 59.1 (CH_2, NBn). The benzylamine (0.75 g, 2.20 mmol) was dissolved in 1,4-dioxane and treated with ethyl chloroformate as described in the general procedure for the synthesis of **4a-d** to give the title compound **6** as an oil. Yield 0.83 g (91%). R_f 0.5 (Et_2O). $[\alpha]_D^{20}$ -20.9 (c 2). ^{1}H NMR (58°C): δ 7.33-7.24 (m, 10H, H-arom), 5.30 (br s, 1H, H-1), 4.70 (AB, 2H, CH_2, NBn, J -14.7 Hz), 4.62 (s, 2H, CH_2, OBn), 4.50 (br d, 1H, H-5), 4.17 (q, 2H, CH_2, Et), 3.90-3.55 (m, 4H, H-3, H-4, H-6), 3.34 (m, 1H, H-2), 1.22 (t, 3H, CH_3, Et). ^{13}C{^{1}H} NMR (58°C): δ 139.0, 137.7 (Cq, arom), 128.1-126.6 (CH, arom), 101.8 (C-1), 81.9, 75.2, 70.2 (C-3, C-4, C-5), 71.7 (CH_2, OBn), 66.4 (C-6), 62.8 (C-2), 61.6 (CH_2, Et), 48.5 (CH_2, NBn), 14.2 (CH_3, Et).

1,6-Anhydro-4-*O*-benzyl-2-benzylamino-2-*N*,3-*O*-carbamate-2-deoxy-β-D-allopyranose (7) - Treatment of compound **6** (0.27 g, 0.64 mmol) with PPh_3 and C_2Cl_6 was executed at 50°C as described in the general procedure to give **7** as a white solid after column chromatography. Yield 0.21 g (86%). R_f 0.4 (Et_2O). $[\alpha]_D^{20}$ +36.7 (c 2). Mp 110°C. ^{1}H NMR: δ 7.40-7.26 (m, 10H, H-arom), 5.43 (d, 1H, H-1, $J_{1,2}$ 0.7 Hz), 4.97, 4.63 (AB, 2H, CH_2, OBn, J -12.3 Hz), 4.81, 4.25 (AB, 2H, CH_2, NBn, J -15.5 Hz), 4.63 (dd, 1H, H-3, $J_{2,3}$ 7.5 Hz, $J_{3,4}$ 1.5 Hz), 4.57 (m, 1H, H-5), 3.58 (dd, 1H, H-6a, $J_{5,6a}$ 5.9 Hz, $J_{6a,6b}$ -8.4 Hz), 3.61-3.56 (m, 2H, H-4, H-6b), 3.50 (dd, 1H, H-2). ^{13}C{^{1}H} NMR: δ 158.2 (C=O), 137.4, 134.7 (Cq, arom), 128.5-127.5 (CH, arom), 96.3 (C-1), 74.6, 72.0, 67.7 (C-3, C-4, C-5), 73.7 (CH_2, OBn), 64.2 (C-6), 55.5 (C-2), 46.3 (CH_2, NBn).

Benzyl 1-amino-3,4,6-tri-*O*-benzyl-1-*N*-ethyloxycarbonyl-β-D-glucopyranoside (8) - Benzyl 1-amino-3,4,6-tri-*O*-benzyl-β-D-glucopyranoside[13] (0.48 g, 0.89 mmol) was treated with ethyl chloroformate as described above to give compound **8** as a white solid. Yield 0.39 g (72%). R_f 0.6 (Et_2O). $[\alpha]_D^{20}$ +12.3 (c 2). Mp 100-101°C. ^{13}C{^{1}H} NMR (58°C): δ 156.8 (C=O), 139.0, 138.6, 138.2 (Cq, arom), 128.2-126.8 (CH, arom), 85.7 (C-1, C-2), 77.5, 77.2, 71.6 (C-3, C-4, C-5), 75.0, 74.6, 73.4 (CH_2, OBn), 68.9 (C-6), 61.8 (CH_2, Et), 46.0 (CH_2, NBn), 14.2 (CH_3, Et).

Benzyl 1-amino-3,4,6-tri-*O*-benzyl-1-*N*,2-*O*-carbamate-β-D-mannopyranoside (9) - Cyclization of compound **8** (0.17 g, 0.28 mmol) with PPh_3 and C_2Cl_6 was executed as described above at 50°C to give **9** after purification on silica gel. Yield 0.14 g (86%). R_f 0.7 (Et_2O/light petroleum, 3/1, v/v). $[\alpha]_D^{20}$ -69.5 (c 1). MS (EI, m/z): 91, 474, 185. ^1H NMR: δ 7.40-7.19 (m, 20H, H-arom), 4.85 (d, 1H, H-1, $J_{1,2}$ 4.3 Hz), 4.82-4.64 (m, 6H, 3x CH_2, OBn), 4.76, 4.18 (AB, 2H, CH_2, NBn, J -14.7 Hz), 4.51 (d, 1H, H-2), 3.82-3.73 (m, 2H, H-3, H-4), 3.65-3.57 (m, 2H, H-6), 3.48 (m, 1H, H-5). $^{13}C\{^1H\}$ NMR: δ 157.2 (C=O), 137.8, 137.6, 137.4, 135.6 (Cq, arom), 128.6-127.6 (CH, arom), 82.0 (C-1), 76.7, 75.2, 74.1, 73.2 (C-2, C-3, C-4, C-5), 74.3, 73.3, 72.2 (CH_2, OBn), 69.3 (C-6), 45.4 (CH_2, NBn).

*Typical procedure for the synthesis of compounds **10a-d*** - The commercially obtained amino alcohols in 1,4-dioxane were treated with benzyl chloroformate as described in the preparation of compounds **4a-d**.

(*R*)-1-(*N*-Benzyloxycarbonyl)amino-2-propanol (10a) - R_f 0.3 (Et_2O). $[\alpha]_D^{20}$ -20.5 (c 2.0). ^1H NMR: δ 7.38-7.26 (m, 5H, H-arom), 5.38 (br s, 1H, NH), 5.10 (s, 2H, CH_2, Cbz), 3.90 (br s, 1H, H-2), 3.30 (ddd, 1H, H-1a, $J_{1a,1b}$ -13.7 Hz, $J_{1a,2}$ 6.2 Hz, $J_{1a,NH}$ 3.0 Hz), 3.04 (ddd, 1H, H-1b, $J_{1b,2}$ 7.3 Hz, $J_{1b,NH}$ 5.5 Hz), 2.41 (br s, 1H, OH), 1.17 (d, 3H, H-3, $J_{2,3}$ 6.4 Hz). $^{13}C\{^1H\}$ NMR: δ 156.8 (C=O), 136.0 (Cq, arom), 128.0, 127.7, 127.6 (CH, arom), 66.5 (C-2), 66.3 (CH_2, Cbz), 47.8 (C-1), 20.0 (C-3).

(1*R*,2*S*)-*N*-Benzyloxycarbonyl-norephedrine (10b) - R_f 0.4 (Et_2O/light petroleum, 2/1, v/v). ^1H NMR: δ 7.36-7.25 (m, 10H, H-arom), 5.12 (s, 2H, CH_2, Cbz), 4.91 (m, 2H, H-1, NH), 4.12 (m, 1H, H-2), 2.80 (s, 1H, OH), 1.05 (d, 3H, H-3, $J_{2,3}$ 6.8 Hz). $^{13}C\{^1H\}$ NMR: δ 156.3 (C=O), 140.7, 136.3 (Cq, arom), 128.4-126.0 (CH, arom), 75.9 (C-1), 66.7 (CH_2, Cbz), 52.3 (C-2), 14.1 (C-3).

(±)-*trans*-2-(*N*-Benzyloxycarbonyl)aminocyclohexanol (10d) - R_f 0.3 (Et_2O). ^1H NMR: δ 7.32-7.25 (m, 5H, H-arom), 5.09 (s, 2H, CH_2, Cbz), 4.87 (br s, 1H, H-1), 3.32 (m, 1H, H-2), 2.82 (s, 1H, OH), 2.01, 1.68 (m, 4H, H-3, H-6), 1.20 (m, 4H, H-4, H-5). $^{13}C\{^1H\}$ NMR: δ 157.2 (C=O), 136.2 (Cq, arom), 128.4, 128.0 (CH, arom), 74.5 (C-1), 66.8 (CH_2, Cbz), 57.0 (C-2), 34.0, 31.7 (C-3, C-6), 24.5, 24.0 (C-4, C-5).

*Chlorination of compounds **10a-d*** - Treatment of compounds **10a-d** with PPh_3 and C_2Cl_6 was executed as described in the general procedure to give chlorides **11a-d**.

(*S*)-1-(*N*-Benzyloxycarbonyl)amino-2-chloropropane (11a) - R_f 0.6 (Et_2O/light petroleum, 1/1, v/v). $[\alpha]_D^{20}$ +30.4 (c 2.0). MS (FAB, m/s): 228 $[M+H]^+$, 245 $[M+NH_4]^+$, 250 $[M+Na]^+$, 226 $[M+K]^+$. ^1H NMR: δ 7.38-7.25 (m, 5H, H-arom), 5.29 (br s, 1H, NH), 5.12 (s, 2H, CH_2, Cbz), 4.17 (m, 1H, H-2), 3.61 (ddd, 1H, H-1a, $J_{1a,1b}$ -14.3 Hz, $J_{1a,2}$ 7.3 Hz, $J_{1a,NH}$ 4.3 Hz), 3.25 (ddd, 1H, H-1b, $J_{1b,2}$ 7.8 Hz, $J_{1b,NH}$ 5.4 Hz), 1.50 (d, 3H, H-3, $J_{2,3}$ 6.6 Hz). $^{13}C\{^1H\}$ NMR: δ 156.2 (C=O), 136.2 (Cq, arom), 128.3, 127.9, 127.8 (CH, arom), 66.6 (CH_2, Cbz), 57.3 (C-2), 48.5 (C-1), 22.0 (C-3).

(1*S*,2*S*)-2-(*N*-Benzyloxycarbonyl)amino-1-phenylchloropropane (11b) - R_f 0.7 (Et_2O/light petroleum, 2/1, v/v). $[\alpha]_D^{20}$ -45.6 (c 1). MS (FAB, m/s): 304 $[M+H]^+$, 321 $[M+NH_4]^+$, 326 $[M+Na]^+$. ^1H NMR: δ 7.36-7.28 (m, 10H, H-arom), 5.05 (s, 2H, CH_2, Cbz), 4.97 (d, 1H, H-1, $J_{1,2}$ 4.7 Hz), 4.95 (m, NH), 4.26 (m, 1H, H-2), 1.22 (d, 3H, H-3, $J_{2,3}$ 6.6 Hz). $^{13}C\{^1H\}$ NMR: δ 155.4 (C=O), 137.9, 136.3 (Cq, arom), 128.4-127.6 (CH, arom), 66.7 (CH_2, Cbz), 66.2 (C-1), 52.4 (C-2), 18.0 (C-3).

(1*R*,2*S*)-2-(*N*-Benzyloxycarbonyl)amino-1-phenylchloropropane (11c) - R_f 0.6 (Et_2O/light petroleum, 2/1, v/v). $[\alpha]_D^{20}$ -21.0 (c 1). MS (FAB, m/s): 326 $[M+Na]^+$, 321 $[M+NH_4]^+$. ^1H NMR: δ 7.41-7.24 (m, 10H, H-arom), 5.30 (br s, 1H, H-1), 5.12 (s, 2H, CH_2, Cbz), 5.05 (m, 1H, NH), 4.16 (m, 1H, H-2), 1.11 (d, 3H, H-3, $J_{2,3}$ 6.6 Hz). $^{13}C\{^1H\}$ NMR: δ 155.3 (C=O), 137.9 (Cq, arom), 128.5-127.3 (CH, arom), 67.7 (CH_2, Cbz), 66.9 (C-1), 52.8 (C-2), 14.4 (C-3).

(±)-*cis*-2-(*N*-Benzyloxycarbonyl)aminochlorocyclohexane (11d) - R_f 0.8 (Et_2O/light petroleum, 3/1, v/v). Mp 61-63°C. MS (EI, m/z): 91, 108, 267. ^1H NMR: δ 7.38-7.25 (m, 5H, H-arom), 5.10 (s, 2H, CH_2, Cbz), 4.48 (br s, 1H, H-1), 3.87 (m, 1H, H-2), 2.21-1.30 (m, 8H, H-3, H-4, H-5, H-6). $^{13}C\{^1H\}$ NMR: δ 155.2 (C=O), 136.5 (Cq, arom), 128.2, 127.7 (CH, arom), 66.5 (CH_2, Cbz), 63.7 (C-1), 52.4 (C-2), 32.9, 27.0, 24.0, 18.9 (C-3, C-4, C-5, C-6).

References and notes

1. van Delft, F.L.; van der Marel, G.A.; van Boom, J.H. *manuscript in preparation.*
2. (a) van Delft, F.L.; de Kort, M.; van der Marel, G.A.; van Boom, J.H. *Tetrahedron: Asymmetry* **1994**, *5*, 2261. (b) van Delft, F.L.; van der Marel, G.A.; van Boom, J.H. *Carbohydrate Lett.* **1996**, *in press.*
3. (a) Hoeksema, H.; Bannister, B.; Birkenmeyer, R.D.; Kagan, F.; Magerlein, B.J.; MacKellar, F.A.; Schroeder, W; Slomp, G; Herr, R.R. *J. Am. Chem. Soc.* **1964**, *86*, 4223. (b) Magerlein, B.J.; Birkenmeyer, R.D.; Kagan, F. *Antibacterial Agents Chemotherapy* **1966**, 727.
4. van Delft, F.L.; de Kort, M. ; van der Marel, G.A.; van Boom, J.H. *J. Org. Chem.* **1996**, *61*, 1883.
5. Ho, P.-T.; Davies, N. *J. Org. Chem.* **1984**, *49*, 3027.
6. Bringmann, G.; Schneider, S. *Synthesis* **1983**, 139.
7. The trans-substitution of **3a** is reflected in a lower H-6 chemical shift (δ 3.25 ppm) and coupling constant ($J_{6,7}$ 3.0 Hz), than for cis-substituted **3b** (δ 3.60 ppm and $J_{6,7}$ 6.8 Hz). (a) Foglia, T.A.; Swern, D. *J. Org. Chem.* **1969**, *34*, 1680. (b) Futagawa, S.; Inui, T.; Shiba, T. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 3308.
8. Das, J. *Synth. Commun.* **1988**, *18*, 907.
9. (a) Kano, S.; Yokomatsu, S.; Iwasawa, H.; Shibuya, S. *Tetrahedron Lett.* **1987**, *28*, 6331. (b) Sakaitani, M.; Ohfune, Y. *J. Am. Chem. Soc.* **1990**, *112*, 1150. (c) Curran, T.P.; Pollastri, M.P.; Abelleira, S.M.; Messier, R.J.; McCollum, T.A.; Rowe, C.G. *Tetrahedron Lett.* **1994**, *35*, 5409. (d) Williams, L.; Zhang, Z.; Ding, X.; Jouillié, M.M. *Tetrahedron Lett.* **1995**, *36*, 7031.
10. Proof of formation of the positively charged phosphonium complex is found in cyclization of compounds **6** and **8**, which are rapidly converted to baseline material at TLC, followed by slow appearance of respective 2-oxazolidinones **7** and **9**.
11. For instance, see: Szabò, L.; Li, Y.; Polt, R. *Tetrahedron Lett.* **1991**, *32*, 585.
12. Trnka, T.; Černý, M. *Coll. Czech. Chem. Commun.* **1971**, *36*, 2216.
13. Gordon, D.M.; Danishefsky, S.J. *Carbohydr. Res.* **1990**, *206*, 361.

VIII

[Dimethyl(phenylthiomethyl)silyl] methylmagnesium chloride: A Novel Hydroxymethylating Reagent[1]

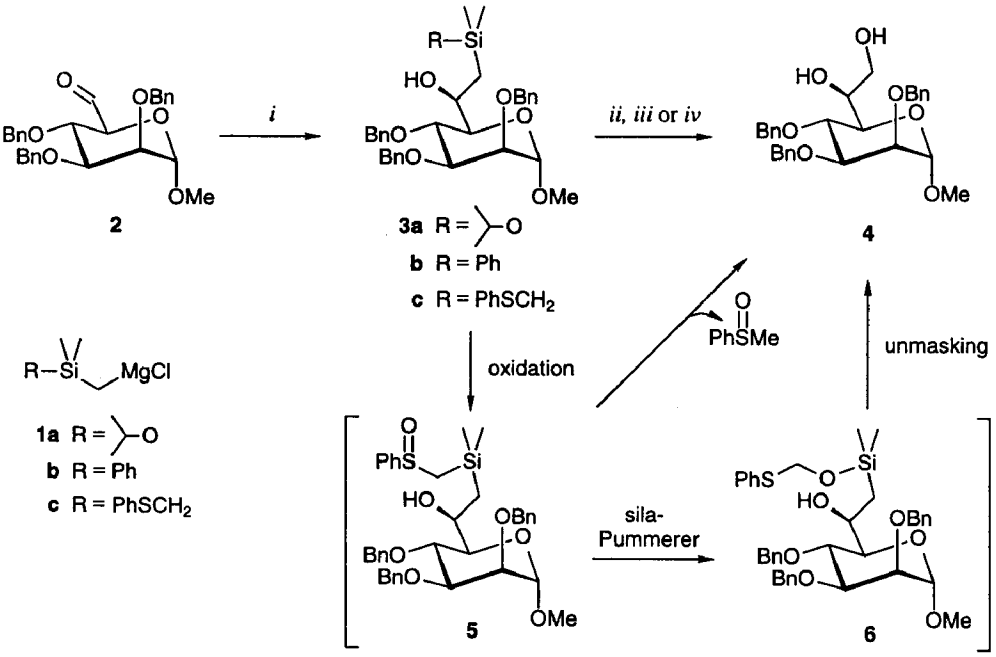
Abstract

The readily accessible hydroxymethylating reagent [dimethyl(phenylthiomethyl)silyl]methylmagnesium chloride (**1c**) reacts smoothly with sugar aldehydes. Mild oxidative cleavage of the C-Si bond in the respective β-amino silane adducts results in the formation of diols in good yield.

Introduction

Earlier studies from this laboratory revealed[2] that the reagent [dimethyl(*iso*-propoxy)silyl]methylmagnesium chloride (**1a**) showed promise for the preparation of the rare sugar L-*glycero*-D-*manno*-heptopyranose (LD-Hep*p*), an essential component of the immunogenic capsular oligosaccharide core of many Gram-negative bacteria. Thus, addition (step *i* in Scheme 1) of **1a** to D-mannose derived aldehyde **2** proceeded with a high degree of diastereoselectivity. Oxidation of the resulting β-hydroxy silane adduct **3a** according to Tamao's procedure[3] (step *ii* in Scheme 1) led to the isolation of the L-*glycero*-D-*manno*-heptopyranoside derivative **4**. The intrinsic lability of the addition product **3a**, however, rendered this approach less attractive for the synthesis of naturally occurring LD-Hep*p* containing oligosaccharides. The latter disadvantage could be circumvented by replacing the *iso*-propoxy group by the more stable phenyl substituent as in reagent **1b**. Consequently, silane adducts resulting from the reaction of **1b** with **2** or derivatives thereof proved to be versatile LD-Hep*p* building units[2b], the dimethylphenylsilyl

Scheme 1



Reagents and conditions

(*i*) **1a-c**, THF, 0°C, 2 h (**3b**: 71%, **3c**: 73%); (*ii*) H_2O_2, KF, $NaHCO_3$, THF, MeOH (R=*i*-PrO: 60% from **2**, R=$PhSCH_2$: 90% from **3c**); (*iii*) KBr, NaOAc, AcO_2H, AcOH, 2 h (72% from **3b**); (*iv*) H_2O_2, KF, SeO_2, $NaHCO_3$, THF, MeOH, 1.5 h (85% from **3c**).

moiety[4] of which can be readily unmasked (*e.g.* conversion of **3b** into **4**) following one of Fleming's procedures[5] (step *iii* in Scheme 1). The merit of the two-step hydroxymethylating protocol was further investigated in chain-extension of other carbohydrate aldehyde[6] or hemiacetal[7] functions. It was found that in most cases nucleophilic addition of **1b** proceeded with high *syn*-stereoselectivity. It was also established[8] that hydroxymethylation of imines with **1b** is feasible by executing the reaction in the presence of cerium or copper salts, which moreover exert a beneficial effect on the stereoselectivity of the process. Despite these attractive features, it is evident that the electrophilic unmasking conditions of Fleming are, in contrast with those of Tamao, not compatible[9] with electron-rich functionalities (*e.g.* internal double bonds or amines).

In order to enlarge the general applicability of silicon-based hydroxymethylating procedures in organic chemistry, we here report that the novel Grignard reagent **1c** derived from (chloromethyl)dimethyl(phenylthiomethyl)silane can be applied successfully for the introduction of the hydroxymethyl function into carbohydrate aldehydes.

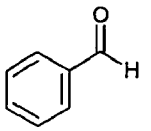
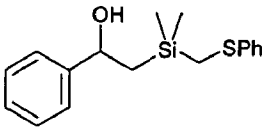
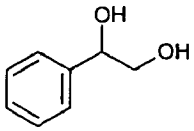
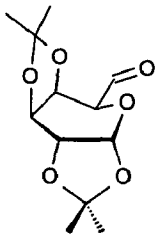
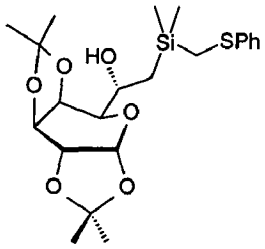
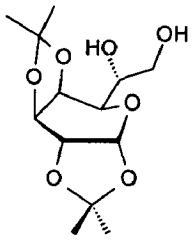
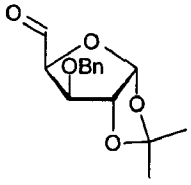
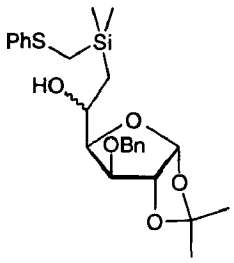
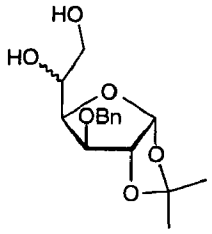
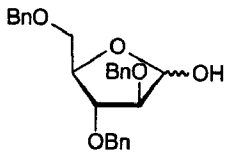
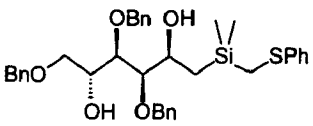
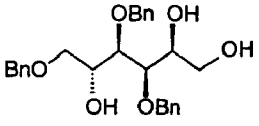
Results and discussion

The design of reagent **1c** was based on the following considerations. Reaction of **1c** with sugar aldehyde **2** would lead to the stable β-hydroxy silane adduct **3c**. Transformation of **3c** into target diol **4** under Tamao conditions would then proceed in three consecutive steps (see Scheme 1): oxidation of **3c** to give sulfoxide **5**, sila-Pummerer rearrangement[10] to product **6** and finally oxidative unmasking of the silyl moiety to give **4**.

The requisite reagent **1c** was readily accessible by metallation of (chloromethyl)dimethyl (phenylthiomethyl)silane[11], prepared in 88% yield from commercially available chloro(chloromethyl)dimethylsilane and phenylthiomethyllithium[12], with magnesium in THF. Addition of **1c** (2.5 equiv.) in THF to aldehyde **2** led, after stirring for 2 h at 0°C followed by work-up and purification, to the exclusive isolation (73%) of the stable *syn*-β-hydroxy silane adduct **3c**, as evidenced by NMR spectroscopy. In the next stage, transformation of **3c** into diol **4** was examined. To this end, **3c** in a mixture of MeOH/THF was subjected to the oxidative unmasking conditions of Tamao[3]. Monitoring of the reaction by TLC revealed slow conversion of **3c** into a more polar product having the same mobility as earlier prepared[2] diol **4**. After stirring at 20°C for 48 h, work-up and purification gave, apart from methyl phenyl sulfoxide, homogeneous **4** (90%), which was in every aspect (NMR, optical rotation) identical with an authentic sample. The failure to detect sulfoxide **5** and (or) rearrangement product **6** indicated that the formation of sulfoxide **5** is the rate-determining step in the Tamao unmasking procedure of **3c**. The latter assumption is endorsed by the finding that unmasking of **3c** to give **4** could be accelerated (reaction was complete in 1.5 h at 20°C) by the addition of an equimolar amount of SeO_2[13] (85% yield). On the other hand, the generation of a near equimolar amount of methyl phenyl sulfoxide is not in accordance with the assumption that unmasking of **3c** takes place *via* sila-Pummerer rearrangement of sulfoxide **5**. Indirect evidence in support of a direct nucleophilic displacement of methyl phenyl sulfoxide from sulfoxide **5** was obtained as follows. Oxidation of **3c** with sodium periodate proceeded slowly to give, after purification, homogeneous sulfoxide **5** which remained unchanged after stirring for several hours at 20°C in a mixture of MeOH/THF. In contrast, treatment of **5** in MeOH/THF with KF-H_2O resulted, as gauged by TLC analysis, in the rapid disappearance of starting material and concomitant liberation of methyl phenyl sulfoxide. Subsequent addition of H_2O_2 and $KHCO_3$ to the above reaction mixture gave, after work-up and purification, diol **4** and the silanol derivative **3** (R=OH).

The versatility of the Grignard reagent **1c** was further evaluated by application of the nucleophilic addition/oxidative unmasking protocol to a variety of aldehydes, the results of which are depicted in Table 1. Thus, condensation of **1c** with benzaldehyde (**7a**) afforded the β-hydroxy silane adduct **8a** in high yield (95%). Oxidation of the C-Si bond in **8a** using Tamao's conditions produced (racemic) styrene glycol (**9a**). Similarly, treatment of galactose aldehyde **7b** with **1c** afforded the *anti*-adduct **8b** as the major product, along

Table 1. Hydroxymethylation of aldehydes **7a-d** with Grignard reagent **1c**.

Aldehyde	β-Hydroxy silane (yield)	1,2-Diol	Yield (time) normal	Yield (time) SeO_2
 **7a**	 **8a** (94%)	 **9a**	88% (5 h)	
 **7b**	 **8b** (44%)[a]	 **9b**	89% (24 h)	84% (1 h)
 **7c**	 **8c** (76%)[b]	 **9c**	87% (30 h) 89%[c] (3 h)	
 **7d**	 **8d** (92%)	 **9d**	87% (48 h)	83% (1.5 h)

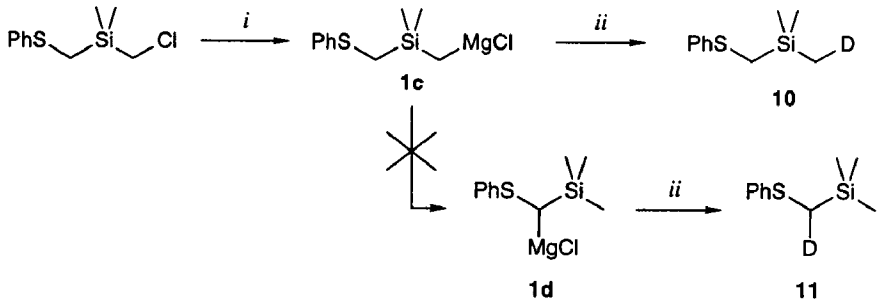
[a]Along with 30% of the *syn*-diastereomer

[b]Obtained as a mixture of *syn*- and *anti*-diastereomers (ratio 20:1)

[c]Reaction performed at 50°C

with 30% of the *syn*-product. The diastereoselectivity of the latter addition is in accordance with results obtained earlier[6c] for the addition of phenylsilane reagent **1b** to the same substrate. Adduct **8b** was oxidatively unmasked to give, after purification on silica gel, diol **9b**[6c] in good yield. Also in this case, the rate of unmasking is significantly enhanced by the equimolar addition of SeO_2. Similar results were obtained by application of the two-step hydroxymethylating procedure to xylose aldehyde **7c** (Table 1). The thus obtained mixture of diastereomers **8c** was subjected to the Tamao unmasking procedure to afford **9c** in high yield. Finally, nucleophilic addition of Grignard **1c** to the anomeric center of arabinose derivative **7d** proceeded only at elevated temperature but with excellent diastereoselectivity. The configuration at C-2 of the resulting β-hydroxy silane **8d** was assigned the *R*-configuration based on earlier observations[7] on the condensation of **7d** with **1b**. Compound **8d** was smoothly unmasked to diol **9d** upon subjection to the H_2O_2-unmasking conditions. The diols **9a-d** were in all aspects identical with the same compounds prepared previously *via* hydroxymethylation using the phenylsilane Grignard reagent **1b**. Finally, the formation of the Grignard reagent **1c** from the corresponding chloride, as well as its stability, were evaluated with the aid of ^{29}Si and ^{2}H NMR spectroscopy. Due to the relatively acidic[14] methylene hydrogen atoms between sulfur and silicon, proton abstraction, after initial formation of the Grignard reagent **1c**, is not excluded. Thus, conversion of **1c** to the secondary and undesired organomagnesium compound **1d** (Scheme 2) might occur. In order to test this assumption, samples were taken from a mixture of the chloride and magnesium in THF (50°C) at different time intervals and quenched with D_2O. After work-up, the respective samples were dissolved in CH_2Cl_2 and analyzed by ^{29}Si NMR spectroscopy at 400 MHz. As depicted in Figure 2, after approximately 2 h the chloride (δ 3.23 ppm) was completely converted into a homogeneous product (δ 1.93 ppm). The sole formation of **1c** and its transformation in **10** was further endorsed by ^{2}H NMR analysis of the product after 2.5 h, showing a single triplet at δ 0.3 ppm.

Scheme 2



Reagents and conditions
(*i*) Mg, THF, 50°C; (*ii*) D_2O.

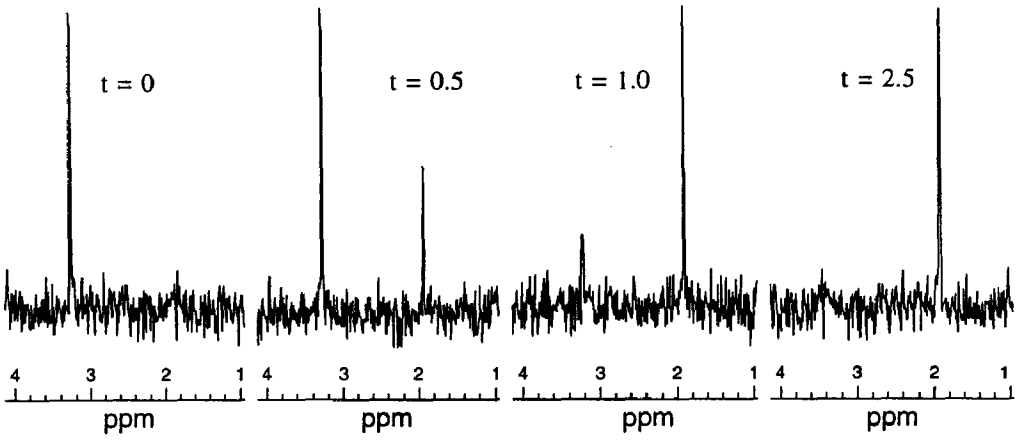


Figure 2. Time-dependent ^{29}Si-spectra of the formation of Grignard reagent **1c** from the chloride and magnesium at 50°C. Samples are obtained by quenching the reaction mixture with D_2O.

Conclusion

The favourable properties of the novel and easily accessible reagent **1c** show great promise for the future stereoselective introduction of hydroxymethyl functions. It is also not excluded that **1c** may be a valuable tool for the chain-extension of carbohydrate imines giving access to amino alcohols.

Experimental

General methods and materials - Tetrahydrofuran and Et_2O were freshly distilled from $LiAlH_4$. Methanol (HPLC-grade, Rathburn) and acetic acid were used as received. All reactions were performed under strictly anhydrous conditions unless noted otherwise. Reactions were followed by TLC analysis on Schleicher and Schüll DC Fertigfolien F 1500 LS 254. Compounds were visualized by UV light (254 nm) and by spraying with 20% sulfuric acid in methanol followed by charring at 140°C. Column chromatography was performed on silica gel 60, 230-400 mesh (Merck). Optical rotations were measured in $CHCl_3$ on a Propol automatic polarimeter. Mass spectra (FAB) were recorded on a Finnigan MAT TSQ70 triple quadrupole mass spectrometer. ^1H NMR spectra and ^{13}C NMR spectra (50.1 MHz) were recorded using a Jeol JNM-FX 200 spectrometer, unless stated otherwise. ^1H NMR spectra (400 MHz) were recorded using a Bruker MSL-400 spectrometer. Chemical shifts (δ) are given in ppm relative to tetramethylsilane as internal standard. Methyl phenyl sulfide was obtained from Aldrich Chem. Co. and distilled before use. Chloro(chloromethyl)dimethylsilane was used as received.

(Chloromethyl)dimethyl(phenylthiomethyl)silane - To a cooled (0°C) mixture of methyl phenyl sulfide (7.03 mL, 60 mmol) in dry Et_2O (200 mL) was added *n*-BuLi (37.5 mL, 1.6 M in hexanes) and the mixture was heated to reflux. After 18 h, solution was cooled to 0°C and with

rapid stirring chloro(chloromethyl)dimethylsilane (5.27 mL, 40 mmol) was added dropwise. The mixture was stirred at rt for 1 h, H_2O (50 mL) was added and the layers were separated. The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residual liquid was vacuum distilled to give (chloromethyl)dimethyl(phenylthiomethyl)silane. Yield 8.13 g (88%). Bp 104-108°C (1.5 mmHg). ^1H NMR: δ 7.30-7.25 (m, 5H, H-arom), 2.90 (s, 2H, CH_2Cl), 2.31 (s, 2H, $SiCH_2S$), 0.27 (s, 6H, $SiCH_3$). $^{13}C\{^1H\}$ NMR: δ 139.2 (Cq, SPh), 128.6, 126.3, 124.9 (CH-arom), 29.2 ($SiCH_2Cl$), 15.4 ($SiCH_2S$), -4.7 ($SiCH_3$). ^{29}Si NMR (neat): δ 3.24.

[Dimethyl(phenylthiomethyl)silyl]methylmagnesium chloride (1c, 1M in THF) - Under a stream of N_2, a small amount of (chloromethyl)dimethyl(phenylthiomethyl)silane (2.31 g, 10.0 mmol) in THF (5 mL) was added to magnesium powder (0.27 g, 11.0 mmol) in a three-neck flask fitted with reflux condenser. The mixture was heated to reflux and the reaction was initiated by the addition of 1,2-dibromoethane (0.1 mL). The remaining solution of the chloride was added at such a rate as to remain a gentle reflux. After the exothermic reaction had subsided, THF (5 mL) was added and the grey-metallic solution stirred at 40°C an additional hour before cooling to rt.

(Phenylthiomethyl)-*d*-trimethylsilane (10) - To a cooled (0°C) solution of **1c** in THF (2 mL, 1 M) was added D_2O (0.5 mL) with vigorous stirring. After 5 min, Et_2O (5 mL) was added and the layers were separated. The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give mono-deuterated (phenylthiomethyl)trimethylsilane. ^1H NMR: δ 7.30-7.09 (m, 5H, H-arom), 2.18 (s, 2H, $SiCH_2S$), 0.16 (s, 8H, $SiCH_3$, $SiCH_2D$). $^{13}C\{^1H\}$ NMR: δ 139.1 (Cq, arom), 128.4, 125.8, 124.4 (CH, arom), 17.9 ($SiCH_2S$), -1.8 ($SiCH_3$). ^{29}Si NMR ($CHCl_3$, 400 MHz): δ 1.94. ^2H NMR ($CHCl_3$, 400 MHz): δ 0.30 (t, J -14.3 Hz).

General procedure for addition of Grignard 1c to aldehyde 2 and 7a-d - An aldehyde (2 mmol) was dissolved in dry THF (10 mL) and cooled to 0°C, before the dropwise addition of a solution of Grignard reagent **1c** in THF (4 mL, 1 M). The solution was stirred for 2 h, diluted with Et_2O (20 mL), quenched with NH_4Cl (5 mL, 15%) and the layers were separated. The organic phase was washed with brine (5 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (elution: Et_2O/light petroleum).

Methyl 2,3,4-tri-*O*-benzyl-6-deoxy-6-dimethyl(phenylthiomethyl)silyl-L-*glycero*-α-D-*manno*-heptopyranoside (3c) - The aldehyde **2c**[6a] (2 mmol) was treated with Grignard **1c** as described in the general procedure. Yield 0.96 g (73%). R_f 0.5 (Et_2O/light petroleum, 2/1, v/v). $[\alpha]_D^{20}$ +18.5 (c 2). ^1H NMR: δ 7.35-7.10 (m, 20H, H-arom), 4.97-4.64 (m, 6H, CH_2, Bn), 4.71 (d, 1H, H-1, $J_{1,2}$ 2.0 Hz), 4.10 (m, 2H, H-4, H-6, $J_{3,4}$ $J_{4,5}$ 9.5 Hz), 3.84 (dd, 1H, H-3, $J_{2,3}$ 3.0 Hz), 3.77 (dd, 1H, H-2), 3.34 (dd, 1H, H-5, $J_{5,6}$ 1.5 Hz), 3.30 (s, 3H, OCH_3), 2.26 (s, 2H, $SiCH_2S$), 1.32 (dd, 1H, H-7a, $J_{6,7a}$ 1.3 Hz, $J_{7a,7b}$ -14.8 Hz), 0.83 (dd, 1H, H-7b, $J_{6,7b}$ 3.6 Hz), 0.21 (s, 6H, $SiCH_3$). $^{13}C\{^1H\}$ NMR: δ 140.0 (Cq, SPh), 138.3, 138.2 (Cq, arom), 128.5-124.4 (CH, arom), 99.3 (C-1), 80.2, 75.3, 75.0, 74.6, 67.0 (C-2, C-3, C-4, C-5, C-6), 75.2, 72.7, 72.0 (CH_2, Bn), 54.6 (OCH_3), 20.5 (C-7), 17.3 ($SiCH_2S$), -2.5, -2.6 ($SiCH_3$).

General procedure for oxidative unmasking of phenylthiomethylsilanes 3c and 8a-d with H_2O_2 - To a solution of a (phenylthiomethyl)silane (1 mmol) in THF (3 mL) and MeOH (2 mL) was added consecutively $NaHCO_3$ (0.20 g, 2 mmol), KF (0.17 g, 2 mmol) and H_2O_2 (0.12 mL, 30% in H_2O). The mixture was stirred at ambient temperature until TLC analysis indicated the

complete disappearance of starting silane and the formation of a more hydrophilic product. Et_2O (10 mL) was added, the mixture was cooled to 0°C and a saturated solution of $NaHSO_3$ (2 mL) was added. The layers were separated and the organic layer was washed with brine (2 mL). The organic phase was dried ($MgSO_4$), filtered and solvents were evaporated. The residue was purified by silica gel column chromatography.

Methyl 2,3,4-tri-*O*-benzyl-L-*glycero*-α-D-*manno*-heptopyranoside (4) - Oxidative unmasking of **3c** (0.12 g, 0.18 mmol) was executed according to the general procedure. Yield 82 mg (90%). R_f 0.3 (CH_2Cl_2/MeOH, 97/3, v/v). $[\alpha]_D^{20}$ +31.2 (c 1.0)(Lit.[2a] +30.5). ^{1}H NMR: δ 7.37-7.23 (m, 15H, H-arom), 4.98-4.62 (m, 6H, CH_2, Bn), 4.69 (d, 1H, H-1, $J_{1,2}$ 1.9 Hz), 4.15 (t, 1H, H-4, $J_{3,4}$ $J_{4,5}$ 11.0 Hz), 3.98 (m, 1H, H-6), 3.88 (dd, 1H, H-3, $J_{2,3}$ 3.0 Hz), 3.78 (dd, 1H, H-2), 3.78 (dd, 1H, H-7a, $J_{6,7a}$ 6.5 Hz, $J_{7a,7b}$ -11.0 Hz), 3.64 (dd, 1H, H-7b, $J_{6,7b}$ 4.0 Hz), 3.59 (dd, 1H, H-5, $J_{5,6}$ 1.5 Hz), 3.26 (s, 3H, OCH_3). ^{13}C{^{1}H} NMR: δ 138.3, 138.2 (Cq, arom), 128.3-127.5 (CH, arom), 99.4 (C-1), 80.0, 74.5, 74.2, 72.3, 69.4 (C-2, C-3, C-4, C-5, C-6), 75.2, 73.0, 72.2 (CH_2, Bn), 64.9 (C-7), 54.8 (OCH_3).

Methyl 2,3,4-tri-*O*-benzyl-6-deoxy-6-dimethyl(phenylsulfinylmethyl)silyl-L-*glycero*-α-D-*manno*-heptopyranoside (5) - Solid $NaIO_4$ (47 mg, 0.22 mmol) was added to a solution of **3c** (0.12 g, 0.18 mmol) in a mixture of MeOH (1 mL) and H_2O (1 mL). The solution was stirred overnight, Et_2O was added (10 mL), the layers were separated and the aqueous phase was extracted with Et_2O (5 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give crude **5** as an off-white solid. Flash chromatography on silica gel (Et_2O→Et_2O/EtOH, 99/1, v/v) afforded **5** as a 1:1 mixture as diastereoisomers (**5** and **5'**). Yield 0.11 g (91%). R_f 0.4 (Et_2O/EtOH, 49/1, v/v). ^{1}H NMR: δ 7.62-7.26 (m, 20H, H-arom), 4.98-4.63 (m, 6H, CH_2, Bn), 4.72 (d, 1H, H-1, $J_{1,2}$ 2.0 Hz), 4.10 (m, 2H, H-4, H-6), 3.84 (dd, 1H, H-3, $J_{2,3}$ 3.0 Hz, $J_{3,4}$ 9.3 Hz), 3.77 (m, 1H, H-2), 3.34 (m, 1H, H-5), 3.28 (s, 3H, OCH_3), 2.72 (d, 0.5H, H-a, $SiCH_2S$, *J* -13.7 Hz), 2.67 (d, 0.5H, H-a', $SiCH_2S$, *J* -13.7 Hz), 2.39 (d, 0.5H, H-b, $SiCH_2S$), 2.34 (d, 0.5H, H-b', $SiCH_2S$), 1.32 (m, 1H, H-7a), 0.85 (m, 0.5H, H-7b), 0.72 (m, 0.5H, H-7b'), 0.25, 0.20 (2x s, 6H, $SiCH_3$). ^{13}C{^{1}H} NMR: δ 147.3 (Cq, SPh), 138.4, 138.3 (Cq, arom), 130.6-123.7 (CH, arom), 99.3, 99.2 (C-1), 80.2, 75.5, 75.4, 75.1, 74.6, 66.5, 66.3 (C-2, C-3, C-4, C-5, C-6), 75.2, 72.8, 72.7, 72.0 (CH_2, Bn), 54.6 (OCH_3), 47.0, 46.6 ($SiCH_2S$), 21.2, 20.9 (C-7), -2.1, -2.3, -2.4 ($SiCH_3$).

Methyl 2,3,4-tri-*O*-benzyl-6-deoxy-6-dimethylhydroxysilyl-L-*glycero*-α-D-*manno*-heptopyranoside (3, R=OH) - Sulfoxide **5** (0.11 g, 0.16 mmol) was dissolved in a mixture of MeOH (1 mL), THF (1 mL) and H_2O (0.2 mL) and was treated with KF (18 mg, 0.32 mmol). The mixture was stirred for 0.5 h, when TLC-analysis (Et_2O) indicated the complete disappearance and the formation of two more lipophilic products (R_f 0.4 and R_f 0.8). Then H_2O_2 (0.20 mL, 30% in H_2O) and $KHCO_3$ (32 mg, 0.32 mmol) were added and the mixture was stirred at rt for 5 h. Et_2O (10 mL) was added, the layers were separated and the organic layer was dried on $MgSO_4$. After filtration, solvents were evaporated and the residual oil applied onto a column of silica gel. Elution was effected with Et_2O/light petroleum (2/1, v/v) followed by Et_2O to give **3** (R=OH). Yield 18 mg (20%). R_f 0.8 (Et_2O). ^{1}H NMR: δ 7.33-7.25 (m, 15H, H-arom), 4.70 (d, 1H, H-1, $J_{1,2}$ 1.9 Hz), 1.25 (m, 1H, H-7a), 0.83 (m, 1H, H-7b), 0.12, 0.11 (2x s, 6H, $SiCH_3$).
Further elution with Et_2O afforded **4**. Yield 43 mg (54%).

2-Dimethyl(phenylthiomethyl)silyl-1-phenyl-ethanol (8a) - Prepared from freshly distilled benzaldehyde (**7a**, 0.21 g, 2.0 mmol) by addition of **1c** according to the general procedure. Yield

0.57 g (94%). R_f 0.4 (Et_2O/light petroleum, 1/1, v/v). ^1H NMR: δ 7.39-7.07 (m, 10H, H-arom), 4.92 (t, 2H, H-1, $J_{1,2}$ 6.8 Hz), 2.11 (s, 2H, $SiCH_2S$), 1.42 (dd, 1H, H-2a, $J_{2a,2b}$ -14.6 Hz), 1.30 (dd, 1H, H-1b), 0.13, 0.09 (2x s, 6H, $SiCH_3$). $^{13}C\{^1H\}$ NMR: δ 146.0 (Cq, Ph), 139.8 (Cq, SPh), 128.4-124.4 (CH, arom), 71.7 (C-1), 26.4 (C-2), 16.9 ($SiCH_2S$), -3.0 ($SiCH_3$).

1-Phenyl-1,2-ethanediol (9a) - Prepared by unmasking of **8a** (0.57 g, 1.89 mmol) according to the general procedure. Yield 0.23 g (88%). R_f 0.3 (Et_2O). $^{13}C\{^1H\}$ NMR: δ 140.9 (Cq, arom), 128.3, 127.7, 126.0 (CH, arom), 74.6 (C-1), 67.9 (C-2).

7-Deoxy-7-dimethyl(phenylthiomethyl)silyl-1,2:3,4-di-*O*-isopropylidene-L-*glycero*-α-D-*galacto*-heptopyranose (8b) and its C-6 epimer - Prepared from aldehyde **8b**[6c] (0.52 g, 2 mmol) by addition of **1c** according to the general procedure. Elution on silica gel was effected with Et_2O/light petroleum (1/3, v/v) to give the D-*glycero*-epimer. Yield 0.27 g (30%). R_f 0.6 (Et_2O/light petroleum, 1/1, v/v). $[\alpha]_D^{20}$ -52.2 (c 1.0). Mp 66-68°C. ^1H NMR: δ 7.30-7.06 (m, 5H, H-arom), 5.58 (d, 1H, H-1, $J_{1,2}$ 5.1 Hz), 4.55 (dd, 1H, H-3, $J_{2,3}$ 2.3 Hz, $J_{3,4}$ 7.9 Hz), 4.30 (2x dd, 2H, H-2, H-4, $J_{4,5}$ 1.9 Hz), 4.07 (m, 1H, H-6), 3.48 (dd, 1H, H-5, $J_{5,6}$ 5.8 Hz), 2.84 (s, 1H, OH), 2.30, 2.29 (2x s, 2H, $SiCH_2S$), 1.54, 1.45, 1.33 (3x s, 12H, CH_3, isoprop), 0.29, 0.25 (2x s, 6H, $SiCH_3$). $^{13}C\{^1H\}$ NMR: δ 139.9 (Cq, arom), 128.5, 125.9, 124.4 (CH, arom), 109.2, 108.6 (Cq, isoprop), 96.4 (C-1), 72.7, 71.7, 70.8, 70.5, 68.6 (C-2, C-3, C-4, C-5, C-6), 26.0, 25.8, 24.9, 24.0 (CH_3, isoprop), 18.7 (C-7), 17.6 ($SiCH_2S$), -2.3, -2.6 ($SiCH_3$). Further elution with Et_2O/light petroleum (1/2, v/v) afforded **8b**. Yield 0.40 g (44%). R_f 0.5 (Et_2O/light petroleum, 1/1, v/v). $[\alpha]_D^{20}$ -48.8 (c 2.0). ^1H NMR: δ 7.31-7.06 (m, 5H, H-arom), 5.55 (d, 1H, H-1, $J_{1,2}$ 5.1 Hz), 4.57 (dd, 1H, H-3, $J_{2,3}$ 2.4 Hz, $J_{3,4}$ 8.0 Hz), 4.44 (dd, 1H, H-4, $J_{4,5}$ 2.0 Hz), 4.30 (dd, 1H, H-2), 4.00 (m, 1H, H-6), 3.47 (dd, 1H, H-5, $J_{5,6}$ 7.3 Hz), 2.50 (d, 1H, OH), 2.29 (s, 2H, $SiCH_2S$), 1.52, 1.46, 1.36, 1.33 (4x s, 12H, CH_3, isoprop), 0.24, 0.22 (2x s, 6H, $SiCH_3$). $^{13}C\{^1H\}$ NMR: δ 140.0 (Cq, arom), 128.5, 126.0, 124.5 (CH, arom), 109.1, 108.4 (Cq, isoprop), 96.3 (C-1), 72.2, 70.7, 70.6, 70.3, 68.4 (C-2, C-3, C-4, C-5, C-6), 25.9, 25.8, 24.8, 24.4 (CH_3, isoprop), 21.0 (C-7), 17.6 ($SiCH_2S$), -2.6 ($SiCH_3$).

1,2:3,4-di-*O*-isopropylidene-L-*glycero*-α-D-*galacto*-heptopyranose (9b) - Oxidative unmasking of silane **8b** (0.20 g, 0.44 mmol) was performed as described in the general procedure to give **9b**. Yield 0.11 g (89%). In another experiment, oxidative unmasking of **8b** (0.20 g, 0.44 mmol) was executed in the presence of SeO_2 (49 mg, 0.44 mmol), added directly after the addition of H_2O_2. Work-up was identical as described above to give **9b** as an oil. Yield 0.10 g (84%). R_f 0.5 (CH_2Cl_2/MeOH, 19/1, v/v). $[\alpha]_D^{20}$ -49.8 (c 1.5)(Lit.[14] -48.0). ^1H NMR: δ 5.48 (d, 1H, H-1, $J_{1,2}$ 5.0 Hz), 4.64 (dd, 1H, H-3, $J_{2,3}$ 2.4 Hz, $J_{3,4}$ 7.9 Hz), 4.45 (dd, 1H, H-4, $J_{4,5}$ 1.8 Hz), 4.32 (dd, 1H, H-2), 3.87 (m, 1H, H-6), 3.75 (m, 3H, H-5, 2x H-7), 1.53, 1.46, 1.37, 1.33 (4x s, 12H, CH_3, isoprop). $^{13}C\{^1H\}$ NMR: δ 109.0, 108.6 (Cq, isoprop), 96.1 (C-1), 70.5, 69.7, 67.2 (C-2, C-3, C-4, C-5, C-6), 63.7 (C-7), 25.8, 24.8, 24.3 (CH_3, isoprop).

3-*O*-Benzyl-6-deoxy-6-dimethyl(phenylthiomethyl)silyl-1,2-*O*-isopropylidene-β-L-idofuranose and 3-*O*-benzyl-6-deoxy-6-dimethyl(phenylthiomethyl)silyl-1,2-*O*-isopropylidene-α-D-glucofuranose (8c) - Grignard addition of **1c** to aldehyde **7c**[6c] (0.50 g, 1.80 mmol) was performed at -20°C as described in the general procedure, to give **8c** as an intractable mixture of *ido*- and *gluco*-diastereomers (ratio 20/1). Yield 0.69 g (76%). R_f 0.7 (Et_2O/light petroleum, 3/1, v/v). ^1H NMR: δ 7.36-7.07 (m, 10H, H-arom), 6.11 (d, 0.05H, $H\text{-}1_{gluco}$, $J_{1,2}$ 3.6 Hz), 5.97 (d, 0.95H, $H\text{-}1_{ido}$, 3.6 Hz), 4.65 (d, 1H, H-2), 4.56 (AB, 2H, CH_2, Bn, J -11.8 Hz), 4.15 (m, 1H, H-5), 3.96 (dd, 1H, H-4, $J_{3,4}$ 3.3 Hz, $J_{4,5}$ 6.3 Hz), 3.89 (d, 1H, H-3), 2.58 (s, 1H, OH), 2.23 (s, 2H, $SiCH_2S$), 1.48, 1.33

(2x s, 6H, CH_3, isoprop), 0.95 (dd, 1H, H-6a, $J_{5,6a}$ 11.1 Hz, $J_{6a,6b}$ -14.3 Hz), 0.66 (bd, 1H, H-6b, $J_{5,6b}$ 1.0 Hz), 0.20, 0.19 (2x s, 6H, $SiCH_3$). $^{13}C\{^1H\}$ NMR: δ 139.9 (Cq, SPh), 136.7 (Cq, Bn), 128.6-124.3 (CH, arom), 111.6 (Cq, isoprop), 104.8 (C-1), 85.4, 82.1, 81.8 (C-2, C-3, C-4), 71.6 (CH_2, Bn), 67.7 ($C\text{-}5_{ido}$), 67.2 ($C\text{-}5_{gluco}$), 26.6, 26.2 (CH_3, isoprop), 21.4 ($C\text{-}6_{gluco}$), 18.9 ($C\text{-}6_{ido}$), 17.4 ($SiCH_2S$), -2.5, -2.7 ($SiCH_3$).

3-*O*-Benzyl-1,2-*O*-isopropylidene-β-L-idofuranose and 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose (9c) - The mixture of epimers **8c** (0.40 g, 0.79 mmol) was treated with H_2O_2 and KF as described in the general procedure to give a mixture of diastereomers **9c**, which were separated on silica gel (Et_2O/light petroleum, 2/1→3/1→1/0, v/v). The first collected fraction was 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose. Yield 98 mg (4%). R_f 0.2 (Et_2O/light petroleum, 3/1, v/v). $[\alpha]_D^{20}$ -44.8 (c 1.0)(Lit.[15] -42). The major fraction collected was the L-idofuranose diastereomer. Yield 0.20 g (83%). R_f 0.1 (Et_2O/light petroleum, 3/1, v/v). $[\alpha]_D^{20}$ -62.0 (c 1.0)(Lit.[15] -64.5). ^1H NMR: δ 7.41-7.22 (m, 5H, H-arom), 5.96 (d, 1H, H-1, $J_{1,2}$ 3.8 Hz), 4.65 (d, 1H, H-2), 4.61 (AB, 2H, CH_2, Bn, J -11.6 Hz), 3.8 (m, 5H, H-3, H-4, H-5, 2x H-6), 1.48, 1.33 (2x s, 6H, CH_3, isoprop). $^{13}C\{^1H\}$ NMR: δ 135.5 (Cq, arom), 128.4, 128.0, 127.7 (CH, arom), 111.7 (Cq, isoprop), 104.6 (C-1), 82.3, 82.0, 79.9 (C-2, C-3, C-4), 71.6 (CH_2, Bn), 70.4 (C-5), 63.1 (C-6), 26.5, 26.1 (CH_3, isoprop). Similar yields were obtained by performing the reaction at 50°C (D-gluco: 5%, L-ido: 84%).

3,4,6-Tri-*O*-benzyl-1-deoxy-1-dimethyl(phenylthiomethyl)silyl-D-glucitol (8d) - 2,3,5-Tri-*O*-benzyl-D-arabinose[16] (1.26 g, 3.0 mmol) was treated at 65°C with Grignard reagent **1c** according to the general procedure. After 1.5 h, the mixture was cooled (0°C) and work-up was executed as described above. Flash chromatography on silica gel (elution with Et_2O/light petroleum, 1/3→1/2, v/v) afforded **8d** as a colorless oil. Yield 1.70 g (92%). R_f 0.4 (Et_2O/light petroleum, 2/1, v/v). $[\alpha]_D^{20}$ -10.3 (c 1.0). ^1H NMR: δ 7.32-7.09 (m, 20H, H-arom), 4.69 (AB, 2H, CH_2, Bn, J -11.6), 4.56 (d, 2H, CH_2, Bn, J -3.2 Hz), 4.53 (s, 2H, CH_2, Bn), 4.01 (m, 2H, H-2, H-5), 3.66 (m, 3H, H-4, 2x H-6), 3.45 (t, 1H, H-3), 2.88 (d, 1H, OH), 2.62 (d, 1H, OH), 2.22 (s, 2H, $SiCH_2S$), 1.18 (dd, 1H, H-1a, $J_{1a,1b}$ -14.6 Hz, $J_{1a,2}$ 9.9 Hz), 1.03 (dd, 1H, H-1b, $J_{1b,2}$ 4.5 Hz), 0.18, 0.17 (2x s, 6H, $SiCH_3$). $^{13}C\{^1H\}$ NMR: δ 140.2 (Cq, SPh), 139.2, 137.9, 137.7 (Cq, Bn), 128.6-124.6 (CH, arom), 84.6, 78.3 (C-3, C-4), 74.9, 73.7, 73.4, 71.2 (C-6, CH_2, Bn), 70.8, 68.6 (C-2, C-5), 20.7 (C-1), 17.6 ($SiCH_2S$), -2.3, -2.4 ($SiCH_3$).

3,4,6-Tri-*O*-benzyl-D-glucitol (9d) - Oxidation of the C-Si bond in **8d** (0.54 g, 0.88 mmol) was performed with H_2O_2 as described above to give triol **9d** as an oil. Yield 0.35 g (87%). ^1H NMR: δ 7.37-7.20 (m, 15H, H-arom), 4.63 (AB, 2H, CH_2, Bn, J -11.4 Hz), 4.56, 4.55 (2x s, 4H, CH_2, Bn), 4.05, 3.93 (2x m, 2H, H-2, H-5), 3.81-3.56 (m, 6H, H-1, H-3, H-4, H-6). $^{13}C\{^1H\}$ NMR: δ 137.7, 137.6 (Cq, Bn), 128.2-127.6 (CH, arom), 79.0, 77.8 (C-3, C-4), 74.1, 73.5, 73.2 (CH_2, Bn), 71.0, 70.8 (C-2, C-5), 70.9 (C-6), 63.9 (C-1).
Executing the reaction in the presence of SeO_2 afforded **9d** in 83% yield.

References and notes

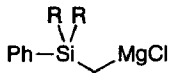
1. Published in part: van Delft, F.L.; van der Marel, G.A.; van Boom, J.H. *Synlett* **1995**, 1069.
2. (a) Boons, G.J.P.H.; van der Klein, P.A.M.; van der Marel, G.A.; van Boom, J.H.

Recl. Trav. Chim. Pays-Bas **1988**, *107*, 507. (b) Boons, G.J.P.H.; Overhand, M.; van der Marel, G.A.; van Boom, J.H. *Carbohydr. Res.* **1989**, *192*, c1-c4.

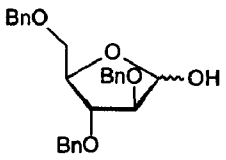
3. (a) Tamao, K.; Ishida, N.; Tanaka, T.; Kumada, M. *Organometallics* **1983**, *2*, 1694. (b) Tamao, K.; Ishida, N.; Ito, Y.; Kumada, M. *Org. Synth.* **1990**, *69*, 96 and references cited therein.
4. For a review on the use of the phenyldimethylsilyl group as a masked hydroxy group, see: Fleming, I.; Henning, R.; Parker, D.C.; Plaut, H.E.; Sanderson, P.E.J. *J. Chem. Soc., Perkin Trans 1* **1995**, 317.
5. (a) Fleming, I.; Henning, R.; Plaut, H. *J. Chem. Soc., Chem. Commun.* **1984**, 29. (b) Fleming, I.; Sanderson, P.E.J. *Tetrahedron Lett.* **1987**, *28*, 4229.
6. (a) Boons, G.J.P.H.; van der Marel, G.A.; van Boom, J.H. *Tetrahedron Lett.* **1989**, *30*, 229. (b) Boons, G.J.P.H.; Overhand, M.; van der Marel, G.A.; van Boom, J.H. *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 1504. (c) Smid, P.; Schipper, F.J.M.; Broxterman, H.J.G.; Boons, G.J.P.H.; van der Marel, G.A.; van Boom, J.H. *Recl. Trav. Chim. Pays-Bas* **1993**, *112*, 451.
7. Smid, P.; Noort, D.; Broxterman, H.J.G.; van Straten, N.C.R.; van der Marel, G.A.; van Boom, J.H. *Recl. Trav. Chim. Pays-Bas* **1992**, *111*, 524.
8. (a) van Delft, F.L.; de Kort, M.; van der Marel, G.A.; van Boom, J.H. *Tetrahedron: Asymmetry* **1994**, *5*, 2261. (b) van Delft, F.L.; van der Marel, G.A.; van Boom, J.H. *Carbohydr. Lett.* **1996**, *in press.*
9. The unfavourable electrophilic conditions can be avoided by following a three-step unmasking approach, see: (a) Taber, D.F.; Yet, L.; Bhamidipati, R.S. *Tetrahedron Lett.* **1995**, *36*, 351, or by the use of a more easily cleavable group on silicon: (b) Stork, G. *Pure & Appl. Chem.* **1989**, *61*, 439. (c) Magar, S.S.; Desai, R.C.; Fuchs, P.L. *J. Org. Chem.* **1992**, *57*, 5360. (d) Chan, T.H.; Nwe, K.T. *ibid.* **1992**, *57*, 6107. (e) Fleming, I.; Winter, S.B.D. *Tetrahedron Lett.* **1993**, *34*, 7287. (f) Norley, M.C.; Kocieński, P.J.; Faller, A. *Synlett* **1994**, 77. (g) Krohn, K.; Kahnbabaee, K. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 99. (h) Hunt, J.A.; Roush, R. *Tetrahedron Lett.* **1995**, *36*, 501. (i) Angelaud, R.; Landais, Y.; Maignan, C. *Tetrahedron Lett.* **1995**, *36*, 3861.
10. Brook, A.G.; Anderson, D.G. *Can. J. Chem.* **1968**, *46*, 2115.
11. A similar strategy was recently reported for oxidative unmasking of (1-phenylthio) cyclopropylsilanes, see reference 9i.
12. Ager, D.J.; Cookson, R.C. *Tetrahedron Lett.* **1980**, *21*, 1677.
13. Drabowicz, T.; Mikolajczyk, M. *Synthesis* **1978**, 758.
14. Dmitriev, B.A.; Chemyak, A.Y.; Chizhov, O.S.; Kochetkov, N.K. *Carbohydr. Res.* **1976**, *47*, 25.
15. Meyer, A.S.; Reichstein, T. *Helv. Chim. Acta* **1946**, *29*, 152.
16. Barker, R.; Fletcher Jr., H.G. *J. Org. Chem.* **1961**, *26*, 4605.

General Discussion

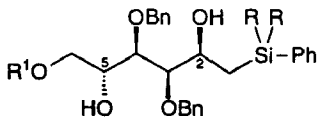
At the onset the primary goal of the work described in this PhD-thesis was to widen the scope of the readily accessible hydroxymethylating reagent **1a** in organic synthesis. Previous results from our laboratory revealed that the Grignard derivative **1a**, a synthetic equivalent of a hydroxymethyl anion, was a useful reagent for the asymmetric transformation of carbohydrate derivatives into higher carbon sugars or aminoglycoside components of antibiotics. Thus, condensation of **1a** with a variety of carbohydrate aldehydes or hemiacetals proceeded in most cases with good stereoselectivity which, in turn, could be controlled by performing the reaction in the presence of stereodirecting additives. Unmasking of the silyl moiety in the resulting adducts could be effected under mild oxidative conditions.



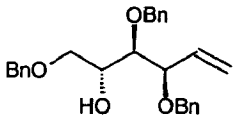
1a R=Me
1b R=*i*-Pr



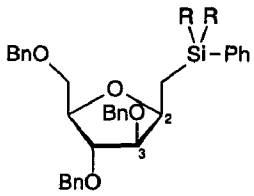
2



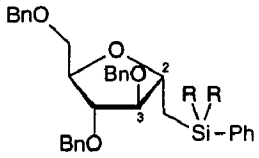
3a R=Me, R^1=Bn
b R=*i*-Pr, R^1=Bn
c R=Me, R^1=H



4



5a R=Me
b R=*i*-Pr



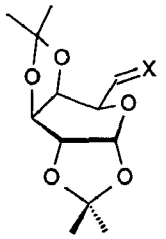
6a R=Me
b R=*i*-Pr

It was envisaged that the Grignard reagent **1a** would be a valuable tool to convert carbohydrates into highly functionalized chiral synthons. To this end, we initially chose the silane **3a**, earlier prepared by us *via* exclusive *syn*-addition of **1a** to the anomeric center of arabinose derivative **2**, as a model compound to achieve this goal. It was expected that acid or base-induced elimination of the β-hydroxy silane moiety in **3a** would give access to the olefin **4**. On the other hand, it was also not excluded that acid treatment of **3a** would follow an alternative pathway, involving intramolecular nucleophilic attack of the C-5 hydroxyl at the intermediate cationic center at C-2, to give the tetrahydrofuran derivatives **5a** or **6a**. Accordingly, compound **3a** was treated (Chapter I) with several

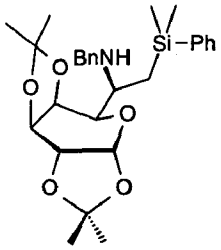
protic and Lewis acids. In all cases, transformation of **3a** into the three possible products **4**, **5a** and **6a** was observed. Interestingly, it was found that the nature of the acid had a profound influence on the stereochemical outcome of the cyclization. Thus, the 2,3-trans product **6a** was formed predominantly using H_2SO_4. In contrast, exclusive formation of the 2,3-cis product **5a** took place upon subjecting **3a** to $BF_3{\cdot}Et_2O$. Similar results were obtained upon acid treatment of β-hydroxy silanes derived from ribose, xylose or the corresponding derivatives lacking the *O*-benzyl function at C-6, *e.g.* triol **3c**. With respect to the existing methodologies for the synthesis of tetrahydrofurans, it was desirable that the competing elimination could be effectively diminished or suppressed. The latter could be achieved by the introduction of bulky *iso*-propyl groups on silicon. Accordingly, Grignard addition of the new reagent **1b** to compound **2**, followed by silylation of the hydroxyl groups and then $BF_3{\cdot}Et_2O$-mediated cyclization, afforded exclusively the tetrahydrofuran product **5b**. Initial attempts to unmask the silyl moiety in **5b** were met with little succes. However, application of the recently reported conditions for oxidation of carbon-silicon bonds using *tert*-butyl hydroperoxide resulted in the formation of the expected alcohol in good yield. It may therefore be concluded that the stereospecific $BF_3{\cdot}Et_2O$-mediated cyclization of 2,5-dihydroxy silanes of type **3b**, readily accessible by diastereoselective addition of di-*iso*-propyl Grignard reagent **1b** to α-alkoxy aldehydes, is a valuable asset in the synthesis of tetrahydrofurans. The latter is supported by the recent acid-mediated cyclization of vinyl- and epoxysilanes reported by Schaumann *et al.* as well as Hosomi *et al.*

The usefulness of the silane adducts of type **1c** for the preparation of 2,5-anhydro-hexitols, based on cyclic sulfate methodology, is illustrated in Chapter II. It was found that base treatment of the readily accessible 2-*O*-acetyl-5,6-*O*-cyclic sulfate derivative of **3c** proceeded *via* intramolecular nucleophilic attack of the *in situ* generated C-2 alkoxide at C-5, to give predominantly a 2,5-anhydro-L-iditol derivative. Although in this case the formation of tetrahydropyran products could not be prevented, it is most likely that the preferred formation of the 5-membered ring will be significantly enhanced starting from non-terminal cyclic sulfates. The latter was endorsed by the fact that exclusive 5-*exo-tet* cyclization occurred in the majority of cases reported by others. In this respect, the complementary procedures, *i.e.* acid-induced cyclization and the use of cyclic sulfates, presented in Chapter I and II are additional tools for the synthesis of 2,5-anhydro-hexitols. Our methodologies may find more general use in the preparation of chiral tetrahydrofurans, which are important constituents of a number of naturally occurring products, *e.g.* polyether antibitiocs and acetogenins.

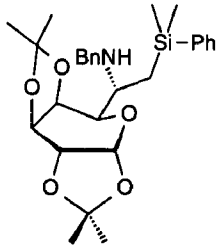
Earlier results indicated that chain-extension of aldehyde **7a** with the Grignard reagent **1a** can be stereocontrolled, *i.e.* selective formation of *syn*- or *anti*-β-hydroxy silane adducts, by executing the reaction in the presence of stereodirecting additives. Further transformation of the adducts led to carbohydrate components of the antibiotics lincomycin



7a X=O
b X=NBn

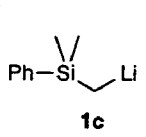


8

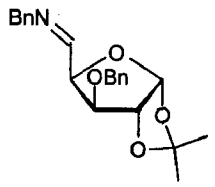


9

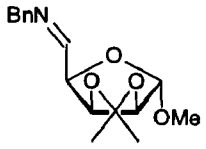
and destomycin, respectively. It occurred to us that a less protracted route to the latter antibiotics would entail nucleophilic addition of **1a** to a C-6 imino derivative of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose, *e.g.* benzylimine **7b**. In Chapter III, it is described that condensation of **1a** to **7b**, in the presence of $CeCl_3$ or $CuI/BF_3{\cdot}Et_2O$ proceeds with excellent diastereoselectivity leading to the *syn*- and *anti*-adducts **8** or **9**, respectively. The latter adducts could be further transformed into precursors of the aforementioned aminoglycosides by a concise and stereoselective route. The merit of nucleophilic chain-extension of carbohydrate imines with Grignard reagent **1a** or its organolithium analogue **1c** for the preparation of aminosugars is further illustrated in Chapter IV and V. Thus, synthesis of the 1-deoxy derivatives of nojirimycin, mannojirimycin and galactostatin could be realized in a stereoselective fashion (Chapter IV) *via* hydroxymethylation of the readily accessible benzylimino sugars **10-12**. Similarly, cerium-mediated addition of **1c** to the glucose-derived ethylimino sugar **13** proceeded with exclusive *syn*-diastereoselectivity to afford, after further processing, the 4-ethylamino sugar of calicheamycin (**14**). The above results indicate that the stereocontrolled hydroxymethylation of α-alkoxy imines in the presence of $CeCl_3$ or $CuI/BF_3{\cdot}Et_2O$, is a valuable attribute *en route* to 1,2-amino alcohols. It is of interest to note that the use of imines avoids the inevitable reduction step required after addition of organometallics to hydrazones, oximes and nitrones.



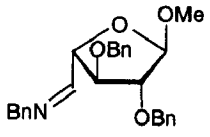
1c



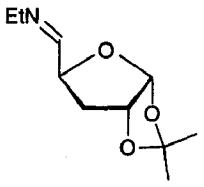
10



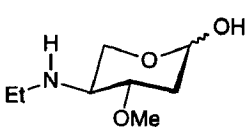
11



12

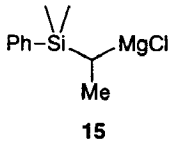


13

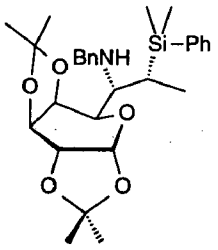


14

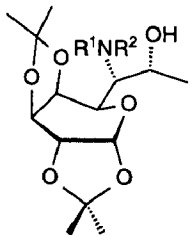
The synthesis of a lincosamine precursor (see Chapter III) could be improved significantly, as shown in Chapter VI, using the novel silyl-based α-hydroxyethylating reagent **15**. Condensation of **15** with the benzylimine **7b**, mediated by $CuI/BF_3{\cdot}Et_2O$, afforded the β-amino silane adduct **16** as a single diastereomeric product in good yield. Protection of the amine function, followed by oxidative unmasking of the silyl moiety (→**17a**) with retention of configuration at C-7 and then hydrogenolysis, gave the lincosamine derivative **17b**. Our route surpasses, in terms of conciseness, stereoselectivity and overall yield, the plethora of other synthetic routes towards lincosamine published so far. The novel reagent **15** seems therefore highly promising for the asymmetric synthesis of β-amino alcohols *via* addition to imines. Furthermore, nucleophilic addition of **15** to α-alkoxy aldehydes may find use in the stereoselective introduction of 1,2-diol systems. It is also not excluded that more silyl-based Grignard reagents, having longer alkyl or functionalized side chains, may be valuable tools for the stereoselective synthesis of alcohols.



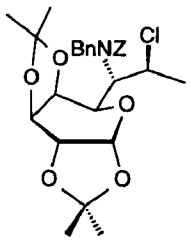
15



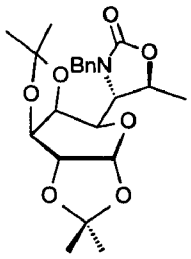
16



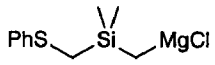
17a R^1=Bn, R^2=Z
b $R^1=R^2$=H



18



19



1d

A related procedure for the synthesis of β-amino alcohols, *via* 2-oxazolidinones, is presented in Chapter VII. An attempt to convert the amino silane adduct **17a**, with triphenylphosphine and hexachloroethane, into the clindasamine precursor **18** led to the exclusive formation of the 2-oxazolidinone derivative **19**. The latter reaction proved to be of general nature, as evidenced by the fact that a similar treatment of other *N*-benzyl,*N*-alkoxycarbonyl protected 1,2-amino alcohols gave in all cases the corresponding 2-oxazolidinones. The stereoselective α-hydroxyethylation of imines and subsequent conversion into 2-oxazolidinones may be a promising route to both *anti* and *syn*-amino alcohols.

Despite the fact that the unmasking of a phenyldimethylsilyl group proceeds under mild oxidative conditions (peracetic acid or *m*-CPBA), the procedure is not compatible with electron-rich functionalities, *e.g.* amines or internal double bonds. On the other hand, an alternative method which comprises the use of hydrogen peroxide, is generally restricted to relatively labile silyl moieties, particularly alkoxysilanes. It was envisaged that the phenylthiomethyl group, as in the Grignard reagent **1d** (Chapter VIII), would combine the merit of a stable silyl moiety with the mildness of the aforementioned oxidative conditions. Thus, addition of the Grignard reagent **1d** to carbohydrate-derived aldehydes proceeded in similar fashion as for **1a**. As expected, subjecting the resulting adducts to hydrogen peroxide in the presence of fluoride ions gave the corresponding diols. In the final stage of my PhD-investigation, Landais *et al.* published a closely related paper on phenylthio(cyclopropyl)dimethylsilanes, unmasking of which could be achieved in a three-step approach involving sila-Pummerer rearrangement. However, in our particular case unmasking proceeds in one step.

Future prospects

Considering the possible negative aspects of the phenylthiomethyl group in the addition of **1d** to imines in the presence of Lewis acids, *e.g.* due to coordination of the acid with lone-pair electrons on sulfur, it seems worthwhile to develop another stable silyl-based hydroxyl equivalent. For instance, it is expected that unmasking of a stable (protected) 3-hydroxypropylsilyl group can be selectively effected *via* deprotection of the hydroxyl function and Brook rearrangement to a propyloxysilyl group which, in turn, can be readily unmasked with hydrogen peroxide.

The latter approach may gain further value by the introduction of a stereogenic center in the 3-hydroxypropyl chain. For instance, an isopropylidene protected 2,3-dihydroxypropyl group is chiral and may therefore be used for enantioselective hydroxymethylation reactions using a silyl-based Grignard reagent of type **1**. It has been shown extensively by Panek *et al.* that α-lithiated silyl reagents containing remote stereogenic centers add highly enantioselectively to carbonyl functions due to intramolecular chelation of the cation.

An alternative future development of the silyl group as a masked hydroxyl may entail unmasking using non-oxidative conditions. Considering the mechanism of the oxidative unmasking (*cf.* Scheme 13, page 11), it may be surmized that other ambiphilic hydroxyl groups that can act both as a nucleophile and an electrophile may serve the same purpose. For instance, it appears worthwhile to investigate the outcome of the treatment of silyl groups, containing a relatively good leaving group, with 2-chloroethanol. If nucleophilic

attack at silicon occurs, it seems likely that rearrangement to the alcohol may occur with concomitant liberation of ethene and chloride anion. Depending on the positive outcome of the latter proposition it may also be forwarded that silyl groups can be converted into other function groups (SH, NH_2) using 2-chloroethanethiol, 2-chloroaminoethane or possibly *O*-arenesulfonylhydroxylamines.

Finally, a completely different potential of organosilanes is found in the field of medicine. Despite the fact that carbon-bound silicon is absent in living organisms, it may not be excluded that the synthesis of silicon-containing analogues of biologically active compounds may find use in the development of novel drugs.

In conclusion, this Thesis presents a contribution to the highly competitive and promising field of silicon in organic synthesis. It provides novel examples of the versatility of silicon, in particular with respect to the β-silicon effect and the oxidation of the carbon-silicon bond.

Samenvatting

Het gebruik van organosilicium-verbindingen in de organische synthese heeft de afgelopen twee decennia een enorme vlucht genomen. Al zijn er geen natuurlijk voorkomende verbindingen bekend met daarin een koolstof-silicium-band, voor de organisch chemicus kunnen silicium-verbindingen van groot synthetisch nut zijn omdat de tijdelijke aanwezigheid van silicium in een organisch molecule een beslissende invloed uit kan oefenen op de uitkomst van een specifieke chemische reactie of transformatie. Als zodanig verschaft het gebruik van silicium de chemicus een bijzonder veelzijdig en nuttig gereedschap voor de totaalsynthese van complexe verbindingen.

Silicium is, na zuurstof, het meest in de aardkorst voorkomende element en is daardoor in ruime mate voorradig. In het periodiek systeem bevindt silicium zich in dezelfde kolom als koolstof en is onder normale omstandigheden ook tetravalent. De verschillen tussen de twee elementen zijn echter groot. Zo vallen organosilicium-verbindingen, oftewel organosilanen, in de klasse der organometalloïden doordat de grotere elektropositiviteit van silicium de onderlinge band polariseert in de richting $Si^{\delta+}$-$C^{\delta-}$. Waar met koolstof eenvoudig dubbele banden zijn te creëren, vormt silicium polymeren met enkele banden. Tot slot vormt silicium zeer sterke banden met zuurstof, chloor en vooral fluor.

Tetra-gealkyleerde organosilanen zijn normaal gesproken stabiele verbindingen die een groot aantal van chemische transformaties kunnen doorstaan. Door een aantal specifieke eigenschappen van silicium echter, kunnen organosilanen een aantal unieke chemische transformaties ondergaan. Zo is het eenvoudig, door de grote stabiliserende werking van silicium (het zogenaamde β-silicium-effect) om op de β-positie van een silylgroup een positieve lading te creëren. Deze stabilisatie valt te verklaren door overlap van de C-Si σ-band, die relatief elektronenrijk is op koolstof, overlapt met de lege naburige π-orbitaal. Aan de andere kant bezit silicium ook het vermogen tot het stabiliseren van negatieve lading die in dit geval waarschijnlijk terug te voeren is op overlap van de vrije elektronen met de relatief elektronen-arme σ^*-antibindende orbitaal op koolstof.

Een andere uniek gegeven beslaat de eigenschap van silicium tot het vormen van extragecoördineerde verbindingen. Behandeling van een organosilaan met een overmaat fluoride-ionen of een andere Lewis-base, resulteert in de vorming van een penta- of hexagecoördineerd deeltje. Dit laatste kan een aantal transformaties ondergaan, zoals omzetting tot een alkylchloride of koppeling met andere halogeenverbindingen met behulp van overgangsmetaal-katalysatoren. Tot slot kan een dergelijk extragecoördineerd silicium onder mild oxidatieve omstandigheden omgezet worden in een hydroxylgroep. Deze laatste eigenschap, alsmede het β-silicium effect, vormden een belangrijke grondslag voor de totstandkoming van dit proefschrift.

In **Hoofdstuk I** en **II** wordt de synthese van 2,5-anhydro-hexitolen, ook *C*-furanosides genaamd, beschreven. Hierbij wordt gebruik gemaakt van het in onze groep ontwikkelde hydroxymethylerend reagens (dimethylphenylsilyl)methylmagnesium-chloride, eenvoudig to bereiden uit (chloromethyl)dimethylphenylsilaan. Wanneer het Grignard-reagens wordt gecondenseerd met hemi-acetalen of aldehydes in suikers, ontstaat, in hoge stereoselectiviteit, een β-hydroxysilaanadduct. In **Hoofdstuk I** wordt aangetoond dat zuurbehandeling van laatstgenoemde verbindingen, als deze een additionele hydroxyl-functie bezitten, resulteert in de vorming van 2,5-anhydro-hexitolen *via* een door het silicium gestabiliseerd kation op de β-positie. De stereoselectiviteit van de cyclisatie kan gestuurd worden door de aard van het zuur. Met het Lewis-zuur $BF_3{\cdot}Et_2O$ is de reactie stereospecifiek en verloopt met retentie van configuratie, terwijl met een katalytische hoeveelheid van een protisch zuur (H_2SO_4) voornamelijk het thermodynamisch meest gunstige produkt wordt gevormd. De ongewenste bijreactie tijdens deze processen, eliminatie van het β-hydroxysilaan tot een dubbele band, kan effectief onderdrukt worden door de introductie van sterisch gehinderde *iso*-propylgroepen op silicium. **Hoofdstuk II** laat zien dat de β-hydroxysilaanadducten, verkregen door additie van bovengenoemd Grignard-reagens op "open-keten" aldehydes, ook op een andere manier omgezet kunnen worden tot 2,5-anhydro-hexitolen, namelijk door intramoleculaire nucleofiele substitutie van cyclische sulfaten. Base-behandeling van de eenvoudig te verkrijgen cyclische sulfaten resulteert voornamelijk of volledig, *via* 5-*exo*-*tet*-cyclisatie, tot het tetrahydrofuran produkt met inversie van configuratie. De hierbij soms optredende vorming van 6-ring-produkten lijkt intrinsiek bepaald door het systeem.

De **Hoofdstukken III** tot en met **VI** laten zien dat behalve ketenverlenging van aldehyde-functies, ook nucleofiele addities op imines mogelijk zijn. **Hoofdstuk III** beslaat het onderzoek van de additie van verscheidene organometalen aan 6-benzylimino-1,2:3,4-di-*O*-isopopylidene-α-D-galactopyranose, eenvoudig te synthetiseren uit D-galactose, in aanwezigheid van $BF_3{\cdot}Et_2O$ en koper(I)-iodide of met cerium(III)-chloride. Hierbij ontstaan, in hoge diastereoselectiviteit, β-aminosilaanadducten met respectievelijk de *anti*- of *syn*-configuratie. Verdere omzetting van deze verbindingen geeft interessante precursors van de aminosuikers lincosamine en destomicine-zuur, die een onderdeel vormen van de antibiotica lincomycine en destomycine. In **Hoofdstuk IV** wordt verder aangetoond dat nucleofiele hydroxymethylering van suikerimines een waardevolle bijdrage kan leveren in de diastereoselectieve synthese van aminoalcoholen. Bijvoorbeeld, de glucosidaseremmers nojirimycine, mannonijinycine en galactostatine, evenals de 1-deoxy analoga, kunnen op een effectieve wijze gesynthetiseerd worden uit eenvoudig verkrijgbare suikerimines. Dezelfde methode wordt toegepast, zoals beschreven wordt in **Hoofdstuk V**, voor de synthese van het 4-ethylaminosuiker van calicheamicine, een veelbelovend, recent geïsoleerd antibioticum met antitumor eigenschappen. Additie van het hydroxymethylerend reagens in aanweigheid van cerium(III)-chloride verloopt volledig diastereoselectief. De

configuratie van het nieuw gevormde stereogene centrum werd ondubbelzinnig vastgesteld met behulp van röntgendiffractie-analyse. **Hoofdstuk VI** beslaat een uiterst stereoselectieve en efficiënte synthese van lincosamine *via* de $CuI/BF_3 \cdot Et_2O$ gestuurde nucleofiele additie van een nieuw α-hydroxyethylerend silyl-reagens. Additie aan het eerder genoemde benzylimino derivaat van galactose resulteert in de vorming van slechts één diastereomeer produkt van de vier mogelijke, met de juiste configuratie op C-6 en C-7. Verdere omzetting tot het aminoalcohol *via* oxidatieve demaskering van de silylgroep, met retentie van configuratie, leidt tot de lincosamine-precursor.

Een additionele methode voor de stereoselectieve synthese van 1,2-aminoalcoholen, *via* 2-oxazolidinon-intermediairen, wordt uit de doeken gedaan in **Hoofdstuk VII**. Er is gevonden dat tijdens de behandeling van *N*-alkyl,*N*-alkyloxycarbonyl beschermde aminoalcoholen met trifenylfosfaan en hexachloorethaan, inversie van configuratie optreedt van het secundaire alcohol, onder vorming van 2-oxazolidinonen. De laatste verbindingen kunnen, door behandeling met base, eenvouding omgezet worden in 1,2-aminoalcoholen.

In **Hoofdstuk VIII** wordt een nieuw hydroxymethylerend reagens met daarin de stabiele fenylthiomethylsilylgroep geïntroduceerd. Oxidatieve demaskering van een dergelijke silyl groep verloopt zeer mild met waterstof peroxide en omzeilt de soms ongunstige oxidatieve condities nodig voor demaskering van de fenylsilylfunctie.

List of Publications

Synthesis of LD-Hep*p* and KDO containing di- and tetrasaccharide derivatives of *Neisseria Meningitidis* inner-core region via iodonium ion promoted glycosidations.
Boons, G.J.P.H.; van Delft, F.L.; van der Klein, P.A.M.; van der Marel, G.A.; van Boom, J.H. *Tetrahedron* **1992**, *48*, 885.

Silicon-directed stereocontrolled cyclization. Possible route to functionalized tetrahydrofurans.
van Delft, F.L.; van der Marel, G.A.; van Boom, J.H. *Tetrahedron Lett.* **1994**, *35*, 1091.

Efficient route to highly functionalized tetrahydrofurans by stereocontrolled silicon-directed cyclization.
van Delft, F.L.; van der Marel, G.A.; van Boom, J.H. *Recl. Trav. Chim. Pays-Bas* **1994**, *113*, 339.

Stereocontrolled hydroxymethylation of carbohydrate imines: formal synthesis of destomic acid and lincosamine.
van Delft, F.L.; de Kort, M.; van der Marel, G.A.; van Boom, J.H. *Tetrahedron: Asymmetry* **1994**, *5*, 2261.

[Dimethyl(phenylthiomethyl)silyl]methylmagnesium chloride. A novel hydroxymethylating reagent.
van Delft, F.L.; van der Marel, G.A.; van Boom, J.H. *Synlett* **1995**, 1069.

Use of a novel α-hydroxyethylating reagent in the stereoselective synthesis of lincosamine.
van Delft, F.L.; de Kort, M.; van der Marel, G.A.; van Boom, J.H. *J. Org. Chem.* **1996**, *61*, 1883.

Hydroxymethylation of carbohydrate imines: formal synthesis of the 4-ethylamino sugar of calicheamycin.
van Delft, F.L.; van der Marel, G.A.; van Boom, J.H. *Carbohydr. Lett.* **1996**, in press.

Curriculum Vitae

Na het behalen van het diploma Gymnasium-β aan het Titus Brandsma Lyceum te Oss in 1986, heb ik in het kader van een jongeren-uitwisselings programma (AFS Interkulturele Programma's) een jaar onderwijs gevolgd op de Mounds View High School te St. Paul, Minnesota, resulterend in het diploma in juni 1987. In september van dat jaar werd begonnen met de studie Scheikunde aan de Rijksuniversiteit Leiden. Het propaedeutisch examen werd in augustus 1988 afgelegd. In de periode van september 1990 tot mei 1991 werd een hoofdvakstage uitgevoerd bij de vakgroep 'Synthese van biopolymeren', onder leiding van prof.dr. J.H. van Boom. Deze stage omvatte de synthese van LD-Hep*p* and KDO-bevattende oligosacchariden uit de inner-core van *Neisseria Meningitidis*. Een tweede onderzoeksstage werd gelopen van februari tot juni 1992 bij de groep Computational Medicinal Chemistry van Organon Int. B.V. te Oss (o.l.v. dr. P.D.J. Grootenhuis). Tijdens deze stage werd onderzoek gedaan naar de geschiktheid van een aantal force fields voor energie-berekeningen aan ring-structuren, en in het bijzonder suikers. Het doctoraal examen werd in augustus 1992 behaald.

Van september 1992 tot mei 1996 was ik als assistent-in-opleiding verbonden aan de Rijksuniversiteit Leiden en werd het in dit proefschrift beschreven onderzoek verricht in de vakgroep van prof.dr. J.H. van Boom. In juli 1994 bezocht ik het "XVIIth International Carbohydrate Symposium" te Ottawa, Canada. In mei 1995 werd deelgenomen aan het "First Symposium on Carbohydrate Mimics" te Strasbourg, Frankrijk en in juli van datzelfde jaar aan het "VIIIth European Carbohydrate Symposium" te Sevilla, Spanje.

Nawoord

Bijna geen enkele grote prestatie is mogelijk zonder hulp van anderen. Deze laatste regels wil ik dan ook wijden aan allen die bijgedragen hebben aan de tot standkoming van dit proefschrift.

Eerst wil ik noemen Caroline Frenay, Martin de Kort en Ragnar Krempel. Zij hebben in het kader van hun doctoraalstudie, ieder op haar of zijn manier, nuttig en belangrijk synthetisch werk gedaan dat terug te vinden is in dit proefschrift. Daarbij heb ik het begeleiden van alledrie als prettig, inspirerend en leerzaam ervaren.

Daarnaast was het goed werken met mijn collega's de afgelopen jaren. Behalve de nuttige chemische discussies, essentiëel voor een degelijke evaluatie van behaalde resultaten en de ontwikkeling van nieuwe ideeën, zou mijn promotie-onderzoek als geheel een stuk minder aangenaam geweest zijn zonder de prima onderlinge sfeer en geregelde sociale activiteiten. In dit verband wil ik mijn zaalgenoten Marco Timmers, Nicole van Straten, Rogier Buijsman en Sander van der Laan graag apart noemen.

Aan de dames van de bibliotheek (Radha, Liesbeth) en de kantine, de heren van de NMR afdeling (Fons, Kees, Johan) en de overige leden van de Gorlaeus die altijd bereid waren tot het verlenen van medewerking, behoud ik goede herinneringen.

Naast de chemie zorgden sociale activiteiten de afgelopen jaren voor een voor mij essentiële compensatie-factor. Geen betere manier om je hersens te ontspannen dan tijdens een wedstrijdje volleybal (SKC of Graficon) of daarna.

Kennissen en vrienden zijn onontbeerlijk in het leven. De luisterende oren, kritische woorden en goede adviezen van mijn moeder, mijn vader, Bart, Paz, en menig ander, ze zijn me veel waard.

Tot slot wil ik Alide noemen, vanwege haar steun en de interesse die zij iedere keer weer op wist te brengen voor mijn 'onwereldse' vaktechnische verhalen. En voor alle uren die ik aan mijn promotie heb besteed en niet aan ons.

 Gedrukt bij Offsetdrukkerij Ridderprint B.V., Ridderkerk